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THE PHYSIOLOGICAL ACTIVITY OF D-THYROXINE

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The human thyroid gland produces only the laevorotatory isomer of thyroxine (Harington and Salter, 1930); D-thyroxine has, however, been produced synthetically and its properties appraised by many workers, using many different methods. All are agreed that its potency is considerably less than that of L-thyroxine, estimates of relative strength varying between 1 : 2 and 1 : ∞.

Estimates of their relative activity in human beings have been few, and much of the earlier work was vitiated by the fact that both preparations were partly racemized. Using purer isomers, Pitt-Rivers and Lerman (1948) found, on the criteria of clinical response and B.M.R., that D-thyroxine had only one-eighth to one-tenth of the potency of L-thyroxine. Starr and Liebhold-Schueck (1953) compared the effects of L-thyroxine, D-thyroxine, triiodothyronine, potassium iodide, and a placebo on the level of protein-bound iodine (P.B.I.) and on the uptake of radio-iodine. Their results were expanded by Starr (1958), and from these two papers some important conclusions may be drawn: (1) that D-thyroxine in a dose five times as great as that of L-thyroxine had an equal effect on the P.B.I.; (2) that by means of a sufficiently large dose of D-thyroxine it was possible to raise the P.B.I. to "thyrotoxic" levels without raising the B.M.R.; (3) that D-thyroxine had very little effect on the level of serum cholesterol; (4) that in hypothyroid patients even a fivefold dosage of D-thyroxine was unable to maintain a B.M.R. stabilized by L-thyroxine; (5) that, whereas the E.C.G. of myxoedematous patients was affected by as little as 0.1 mg. of L-thyroxine, as much as 10 mg. a day of D-thyroxine given for 18 consecutive days was ineffective; (6) that when almost complete suppression of the uptake of radio-iodine was achieved with a given dose of L-thyroxine the same dose of D-thyroxine caused a suppression to only about 40% of the initial uptake; (7) that these results were not vitiated by the iodine content of the thyroxines.

To summarize previous work, it would appear that the effect of D-thyroxine on the metabolic processes considered is extremely slight in comparison with that of L-thyroxine. On the basis of the E.C.G. it may be as little as 1/100 of that of L-thyroxine, and on the basis of the B.M.R. not more than 1/5 and perhaps 1/10. Yet its effect on the uptake of radio-iodine suggests that its depressant effect on the production of thyrotrophic hormone (T.S.H.) is about half that of L-thyroxine.

This observation, if confirmed, suggests several interesting corollaries. For instance, (1) If some forms of hyperthyroidism arise in the pituitary the suppression of the output of T.S.H. (without significant rise in metabolism) by means of D-thyroxine should control the hyperthyroidism. D-thyroxine might prove to be the tool by means of which the primarily thyroid case of thyrotoxicosis could be distinguished from the primarily pituitary case, if indeed two such types exist. (2) If exophthalmos, as is still believed by some despite evidence to the contrary (Greene, 1955; Gilliland and Strudwick, 1956), is due to an excessive production of T.S.H., it should be possible to reduce it by means of D-thyroxine without detriment to the patient.

Experiment I: Clinical Effects of D-thyroxine in Hypothyroidism

In the earlier cases, treatment was begun cautiously with a dosage of 0.25 mg. daily, gradually increased at fortnightly intervals to allow observations to be made at each dosage level. As experience has accumulated the initial dose has been raised.

Eight patients, diagnosed clinically and by laboratory tests as suffering from hypothyroidism, have been treated with D-thyroxine. The results were as follows.

Case 1.—Fibrosis of the thyroid and severe myxoedema. The patient became euthyroid when treated with D-thyroxine in a dosage of 8 mg. daily for a fortnight, and has since remained well on 0.4 mg. daily of L-thyroxine. The ratio of potency of L-thyroxine to D-thyroxine (L : D) is in this case 20 : 1.

Case 2.—Mild hypothyroidism with impalpable thyroid. She became euthyroid after 4 mg. daily of D-thyroxine had been administered for a fortnight, and has since been maintained in good health with 0.4 mg. of L-thyroxine. L : D = 10 : 1.

Case 3.—Hashimoto's disease and extreme myxoedema. Improvement did not begin until D-thyroxine, 20 mg. daily, had been given for a fortnight. L-thyroxine has now been prescribed in a dosage of 0.5 mg. L : D = 40 : 1.

Case 4.—Moderate myxoedema with impalpable thyroid. Ten mg. of D-thyroxine administered for a fortnight had no effect. She has since been maintained in good health with 0.5 mg. daily of L-thyroxine. L : D = >20 : 1.

Case 5.—Large diffuse goitre with mild clinical hypothyroidism. She responded in a fortnight to 10 mg. daily of D-thyroxine and has since been kept well with L-thyroxine 0.2 mg. daily. L : D = 50 : 1.

Case 6.—Nodular goitre with mild hypothyroidism. She was relieved by 10 mg. daily for a fortnight, and has since remained well with L-thyroxine 0.4 mg. daily. L : D = 25 : 1.

Case 7.—Moderate post-operative hypothyroidism. D-thyroxine 15 mg. daily for a fortnight had no effect. L-thyroxine was effective in a dosage of 0.5 mg. daily. L : D = >30 : 1.

Case 8.—Severe post-operative hypothyroidism. 15 mg. daily of D-thyroxine for a fortnight relieved her and she has remained well with 0.3 mg. daily of L-thyroxine. L:D=50:1.

Results of Experiment I

These figures are admittedly meagre, but they support the contention of previous authors that the metabolic effects of D-thyroxine, judged by clinical means, are very slight, the most responsive patient having an "L:D ratio" of 10:1. In the majority of patients it appears that the ratio is far higher, and may be as high as 50:1 or more. Neither the B.M.R. nor the serum cholesterol was measured consistently in a sufficient number of patients for firm conclusions to be drawn, but in no patient was a rise in the former or a fall in the latter observed with a daily dose of less than 4 mg. In 6 of the 8 cases, 10 mg. or more was needed. The serum cholesterol (*pace* Starr, 1958) appeared to fall when the clinical condition was corrected.

Experiment II: Effect of D-thyroxine on the Immediate Thyroidal Uptake of Radio-iodine

In the earlier cases, numbering 10, the slope "S" of the immediate uptake of ^{132}I (Farran, 1958) was measured before the administration of D-thyroxine and afterwards at fortnightly intervals during its administration in various doses.

(*a*) Four of the patients were originally euthyroid by all criteria. A suppression of iodine uptake occurred with a dose of 1 mg. daily of D-thyroxine in three cases (two with single "hot" nodules, and one with slight diffuse thyroid enlargement). In one patient with a multinodular goitre no suppression occurred with either D-thyroxine (1 mg.) or L-thyroxine (0.3 mg.). One of the patients with a single "hot" nodule showed suppression of iodine uptake with a dose of 1 mg. of D-thyroxine but no suppression with 0.2 mg. of L-thyroxine.

(*b*) Six of the patients were thyrotoxic and deserve more detailed consideration.

Case 9.—Severely toxic diffuse goitre with severe exophthalmic ophthalmoplegia. The uptake expressed as "S" on 0.25 mg. daily of D-thyroxine was temporarily suppressed from 3.4 to 0.85; 1 mg. daily of D-thyroxine was needed to maintain it at this level. In 10 months no change in the eyes or in the degree of thyrotoxicosis occurred, and it was necessary to treat the exophthalmos with *x* rays to the orbits and the thyrotoxicosis with carbimazole. L-thyroxine 0.3 mg. daily failed to suppress the uptake (see Fig. 1).

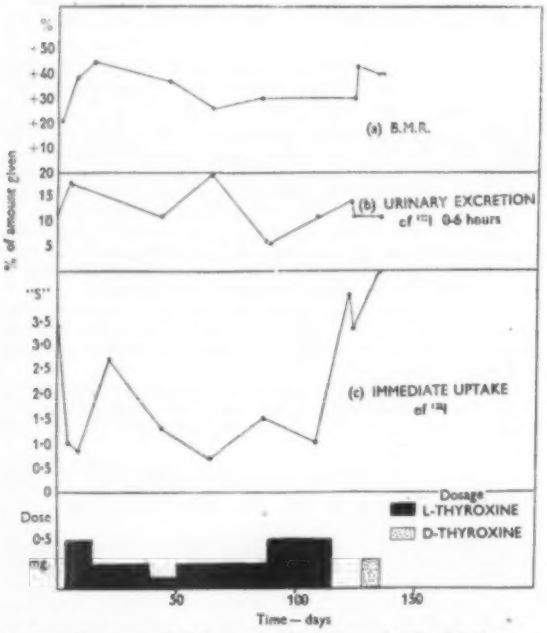

FIG. 1.—Response of Case 9 to varying dosage levels of D-thyroxine. (*a*) B.M.R. (*b*) Urinary excretion of ^{132}I during 0–6 hours. (*c*) "S."

Case 10.—Severely toxic diffuse goitre, with severe exophthalmic ophthalmoplegia, acropachy, and pretibial myxoedema. D-thyroxine 0.5 mg. suppressed S from 2.8 to 1.1, but only temporarily; 1 mg. failed to produce any further depression, and it was necessary to terminate the experiment and give *x*-rays to the orbits and carbimazole.

Case 11.—Slight thyrotoxicosis with impalpable thyroid and exophthalmos. D-thyroxine 0.5 mg. daily produced suppression of S from 2.8 to 1.1; but an increase in dosage to 1 mg. produced no further depression or clinical change, and the experiment was discontinued after three months.

Case 12.—Slight thyrotoxicosis with slightly enlarged thyroid and exophthalmos and a thyroid index ("T") of 24. D-thyroxine in a dosage of 0.5 mg. daily suppressed S to 0 in four weeks; 1 mg. was required to maintain depression, but on stopping treatment S rose to 1.2. No clinical changes occurred.

Case 13.—This and the next case are worthy of special consideration. Case 13 was a male suffering from severe thyrotoxicosis judged by clinical standards. He had a slightly enlarged diffuse goitre, a severe but stationary degree of exophthalmos, a B.M.R. of +24%, a characteristic E.C.G., and pretibial myxoedema. T was 29. D-thyroxine in a dose of 0.25 mg. daily raised gradually to 1 mg. had no effect, but after a fortnight on 1 mg. a slight suppression of uptake occurred, and after 14 weeks the value of S sank gradually from 1.8 to 0. During this time his clinical condition steadily improved and at the end he was clinically euthyroid. His weight had increased by 12 lb. (5.44 kg.) and his B.M.R. had dropped to +11%. Treatment was stopped without, during nine months of clinical observation, any detriment to his clinical condition. Throughout there was no significant change in his exophthalmos, but his pretibial myxoedema disappeared (Fig. 2).

Case 14.—This case also deserves special consideration. It was that of a young woman with severe recurrent thyrotoxicosis four

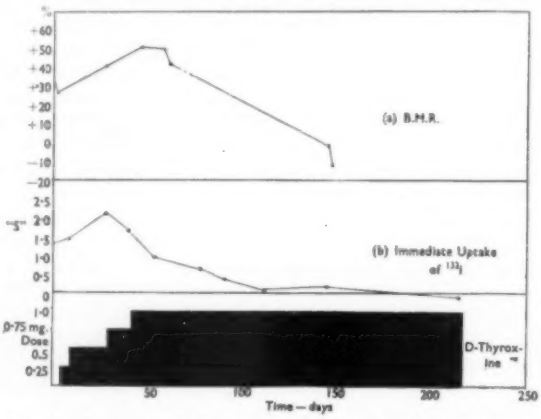

FIG. 2.—Response of Case 13 to treatment with D-thyroxine. (*a*) The effect on the B.M.R. (*b*) "S."

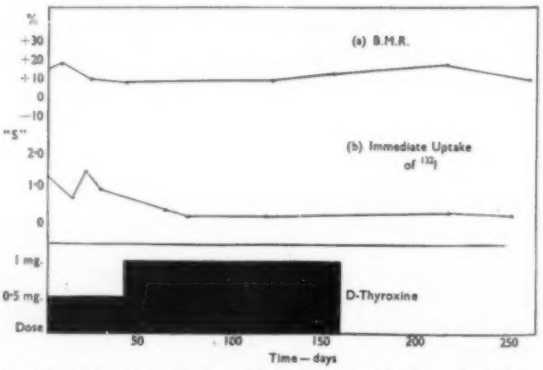

FIG. 3.—Response of Case 14 to treatment with D-thyroxine. (*a*) The effect on the B.M.R. (*b*) "S."

years after thyroidectomy, with severe and recently progressive exophthalmos. The B.M.R. was +21%. D-thyroxine in a daily dosage of 0.5 mg. reduced the value of S from 1.6 to 0.75. The dose was gradually raised to 1 mg. daily and the value of S dropped to 0.2. During five months she steadily improved and became clinically euthyroid, with a B.M.R. of +9%. There was no change in the degree of exophthalmos. When seen six months later she remained well (Fig. 3). It would appear, therefore, that 1 mg. daily of D-thyroxine suppressed the uptake of radio-iodine in all these six thyrotoxic patients, albeit temporarily in two. In two, a complete remission of thyrotoxicosis occurred during treatment with D-thyroxine, but in neither was any improvement in exophthalmos observed.

Summary of Results of Experiment II

Of 10 patients—6 thyrotoxic, 4 euthyroid—9 showed a depression of uptake of radio-iodine, most with doses as low as 0.25 mg. daily of D-thyroxine. However, in the majority a daily dosage of 1 mg. was necessary for suppression to be maintained. The only patient in whom suppression did not occur had a multinodular goitre without evidence of either hyperthyroidism or hypothyroidism. A daily dose of 0.3 mg. of L-thyroxine likewise failed to suppress uptake, though, unlike D-thyroxine, it rendered the patient thyrotoxic.

Two patients are worthy of particular stress. Both were suffering from thyrotoxicosis with exophthalmos. A daily dose of 1 mg. of D-thyroxine apparently rendered them euthyroid but failed to improve their exophthalmos. Though the operation of chance cannot be excluded, it is difficult to escape the conclusion that in these two patients the thyrotoxicosis was due to an excessive production of T.S.H. and that the exophthalmos was not, in the period of observation, relieved by its reduction.

Experiment III: Effect of D-thyroxine on the Discharge of Radio-iodine from the Thyroid

The first experiment having shown that 1 mg. of D-thyroxine was sufficient to produce an effect on the uptake, it was decided that the discharge of radio-iodine from the thyroid would perhaps be a more reliable index of the suppression of T.S.H. production. In 12 cases ^{131}I was given orally, 50 μc to patients under 45 and 200 μc to older patients about to undergo treatment with radioactive iodine. After 48 hours, treatment was begun with carbimazole in a dosage of 20 mg. eight-hourly, given in order to prevent re-use of circulating iodide by the thyroid. This drug was chosen instead of potassium perchlorate, which might from some points of view be considered preferable, because in our clinic it is normally used for the preparation of thyrotoxic patients for thyroidectomy and often for therapy with radioactive iodine. Thenceforward counts over neck and thigh were made twice daily, using a partially collimated, wide-angle scintillation counter with an efficiency of about 10 counts per second per μc in the neck. The counting rate over the neck, minus that over the thigh, was plotted against the time in hours, using semilogarithmic paper, so that the biological half-life of the radioactive iodine in the thyroid could be plotted as a straight line. The slope of this line could usually be determined after three or four days, though in one or two cases six or seven days were necessary. When the initial slope had been determined, 1 mg. of D-thyroxine was given daily for 5–10 days, counts twice daily continuing.

Results of Experiment III

An immediate effect of D-thyroxine was observed in 5 of the 12 cases. In 5 cases no discernible change in the slope occurred during the succeeding 7 to 14 days (Figs. 4 and 5). In two cases the initial biological half-life was so long that the results could not be assessed.

An analysis of the characteristics of the five "successful" cases gives no indication of any which clearly differentiates them from the "unsuccessful" cases. All patients in both groups were thyrotoxic, most of them severely. Both groups contained examples of diffusely enlarged and nodular goitres with various degrees of enlargement, and

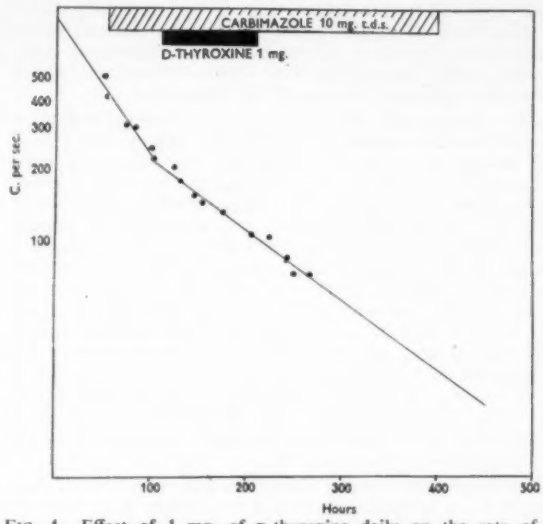

FIG. 4.—Effect of 1 mg. of D-thyroxine daily on the rate of discharge of ^{131}I from the thyroid. Showing suppression of T.S.H.

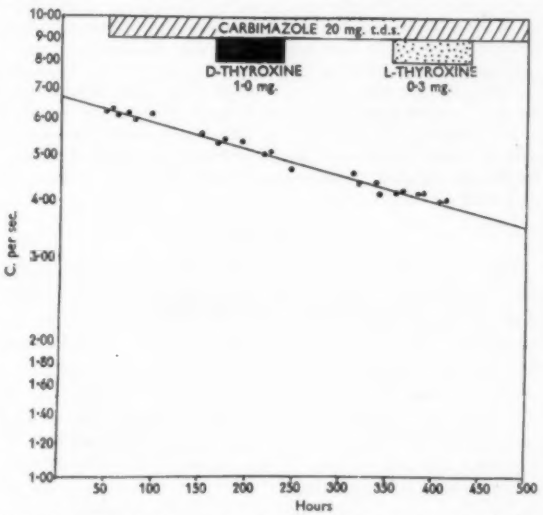

FIG. 5.—Effect of 1 mg. of D-thyroxine daily on the rate of discharge of ^{131}I from the thyroid. Showing no apparent effect on T.S.H. production.

of exophthalmos. It is clear that if any clinical difference exists between the two groups a larger series must be examined before it becomes manifest.

Discussion

The results of these experiments give support to previous work and strongly suggest that D-thyroxine has a very weak effect upon tissue metabolism. A numerical estimate of the relative potency of D-thyroxine and L-thyroxine cannot be made at present, but it appears that L-thyroxine is at least 10 times as effective as D-thyroxine by any criterion, and the figure may well be higher. On the other hand, small doses of D-thyroxine have, even in thyrotoxicosis, a suppressive effect on the thyroidal uptake and discharge of radio-iodine and, it may be inferred, upon the production of T.S.H. by the anterior pituitary. This finding is surprising. Werner *et al.* (1952) failed to suppress by means of desiccated thyroid the radio-iodine uptake of thyrotoxic patients. Morgans *et al.* (1952) reported a like failure using L-thyroxine, and Werner and Hamilton (1953) using triiodothyronine. The fact that in two of our patients suppression

was produced by D-thyroxine but not by L-thyroxine might suggest that D-thyroxine has a qualitatively different effect from that of L-thyroxine on the anterior pituitary. This seems highly improbable, and further work with both isomers is necessary to resolve the dilemma.

The expectation that cases of thyrotoxicosis might be found in which it would be possible to reduce the metabolism to normal by means of D-thyroxine has apparently been fulfilled in two of six patients treated for three months. This is not so surprising, for Means (1948) has reported a clinical improvement in cases of Graves's disease treated with desiccated thyroid, and Werner *et al.* (1952) quote a single case personally communicated to them by Greer. Moreover, these authors noted that in several of their patients treatment with thyroid was accompanied by a fall in the level of P.B.I. They advanced three possible causes for this finding—the effects of non-hormonal iodine in the desiccated thyroid, of repeated doses of ^{131}I, or of rest in bed. None of these explanations is applicable in our patients. Moreover, the danger to the patient of using thyroid or L-thyroxine is absent when the relatively non-calorigenic D-thyroxine is used.

Although the output of T.S.H. was inhibited, at least temporarily, in almost every case in our series, in no instance was any change seen in the degree of exophthalmos. This observation cannot be explained by the hypothesis that exophthalmos, originally produced by an excess of T.S.H., has become irreversible, for it is a common observation that exophthalmos may decrease or even disappear spontaneously. The doses of D-thyroxine used, smaller than in the hypothyroid patients, were large enough to depress the uptake of radio-iodine for periods up to 10 months, but not large enough to increase metabolism. Our results give support to those who have long doubted the classical hypothesis that exophthalmos is due to an excessive production of T.S.H. by the pituitary.

Summary

The metabolic effects of D-thyroxine are very slight when compared with those of L-thyroxine, the latter being at least ten times as potent. On the other hand, doses of D-thyroxine too small to effect metabolism directly are capable in most cases, even of thyrotoxicosis, of suppressing the uptake of radio-iodine and, by inference, the production of T.S.H. Suppression of the production of T.S.H. appeared to induce a remission of Graves's disease in two of six patients, but the exophthalmos was not improved.

We are grateful to other members of the staff of the department of endocrinology of New End Hospital for allowing access to their patients, and to Dr. A. W. G. Goolden for much helpful advice. Glaxo Laboratories Ltd. have most generously supplied all the D-thyroxine used.

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The fourth annual "Aircent" medical conference, dealing with aviation medicine and the medical aspects of nuclear warfare against air bases, was held at Headquarters, Allied Air Forces Central Europe, Fontainebleau, from October 8 to 10. Group Captain E. S. SIDEY, Medical Branch of the R.A.F., presided. Over 50 delegates attended, including senior officers from the Medical Services of the armed Forces of the United Kingdom, the United States, Canada, France, Belgium, the Netherlands, West Germany, and Italy.

THE IMMEDIATE UPTAKE OF RADIOACTIVE IODINE AS A TEST OF THYROID FUNCTION

BY

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The rate of uptake of radioactive iodine by the thyroid has been used as the basis of a number of tests of thyroid function (Myant, Pochin, and Goldie, 1949; Astwood and Stanley, 1947; Goolden, 1958). It is commonly agreed that in about 90% of the cases tested a good separation can be achieved between thyrotoxic and euthyroid patients with an overlap of 5 to 10% whichever method is adopted. The technique reported here has been found of value when an answer is needed immediately or when serial investigations are required on the same person. The radiation dose is extremely small, particularly when ^{132}I is used.

Material and Method

Four scintillation counters with sodium iodide crystals, 1½ in. (3.8 cm.) diameter and 1 in. (2.5 cm.) long, are used. Each crystal is backed by a perspex light guide, 1½ in. (3.8 cm.) in diameter and ¼ in. (1.9 cm.) long, which forms the optical connexion to a photomultiplier. The pulses from the four counters are fed into a mixer unit and from there, through an amplifier, to a ratemeter which is connected to a pen recorder (Fig. 1). The counters are mounted in cylindrical lead shields 2 in. (5 cm.) thick, which are positioned so as to form a ring 20 cm. in diameter. The patient is seated in a dental chair, which can be adjusted

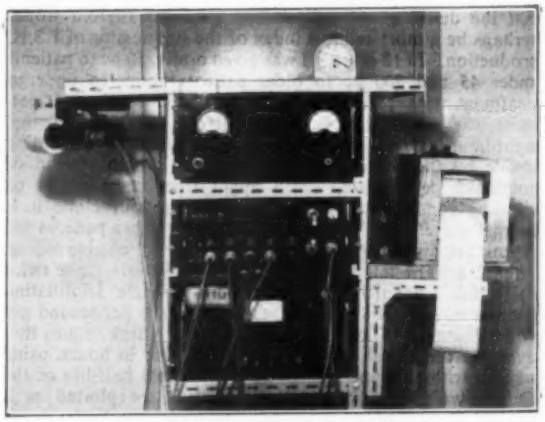

FIG. 1.—General view of the equipment.

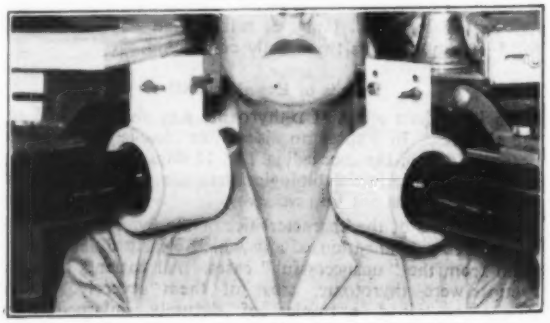

FIG. 2.—The counters in position round the patient's neck.

so that the counters are at the level of the thyroid (Fig. 2). The pen recorder is started as soon as the patient is comfortably settled and measures the background radiation under the conditions of the test. When serial tests are made this recording can be used to correct for any residual activity in the neck due to previous investigations. Normal saline containing 3–5 μc of either ^{131}I or ^{132}I is injected intravenously, and the uptake of the radioactive iodine is continuously recorded for 30 minutes after the injection is given. The recording is continuous, but, if necessary, ill or nervous patients can be released from time to time and intermittent readings made on the recording, which continues to run until the test is finished.

Calculation of Results

The uptake of iodine by the thyroid is dependent partly on renal clearance and partly on the rate of diffusion into the extracellular tissues. Various mathematical expressions have been suggested to fit these conditions (Oddie, 1949; Berson *et al.*, 1954, 1955; Larsson, 1955). Astwood and Stanley (1947) found empirically that the activity in the thyroid plotted against the square root of time resulted in a straight line, and this convention has been adopted here. The counting rate is taken from the recording and replotted against the square root of the time in minutes. The resultant straight line is extrapolated back to the time of the injection to find the counting rate at zero time (C_0). The result of the test is then expressed as an arbitrary quantity "S," which is calculated from the formula: $S = \frac{C_{25} - C_0}{C_0}$

where C_{25} is the counting rate 25 minutes after the injection. S is thus independent of the amount of activity given.

C_0 varies slightly with the size and shape of the person being investigated, since it is a measure of the proportion of the activity which is seen by the counters, and is of the order of 80–100 counts per second per μc of ^{131}I injected; 1 μc of ^{132}I gives twice this counting rate. The background counting rate before any activity is given is usually 120–150 counts per second, and the efficiency of the counters is such that 1 μc of ^{131}I gives 800 counts per second and 1 μc of ^{132}I nearly 2,000 counts per second. Small variations in the position of the source make very little difference to the counting rate.

In patients suffering from severe thyrotoxicosis this graph of the uptake does not remain a straight line even for the first 25 minutes, and in these cases C_0 is calculated from the initial straight portion of the curve; but the actual value of C_{25} is used, so that the value for S is less than would be expected from the initial rate of uptake. C_0 is proportional to the extrathyroidal activity, which decreases during the test owing to clearance of the radioactive iodine by the thyroid and kidneys. In patients whose thyroids concentrate little or no iodine, either because they are hypothyroid or because of the administration of antithyroid drugs, S has a negative value.

Results

Tests of thyroid function have been made on 357 subjects in whom the clinical diagnosis is reasonably certain. The criterion for selection has been the expressed opinion of two independent clinicians, or, when this has not been available, the opinion of one clinician when that opinion has been subsequently confirmed by laboratory tests or by a therapeutic trial of antithyroid drugs, usually carbimazole. In 50 of the patients 10 μc, or more, of ^{131}I has been given and measurements made of the radioactivity in the urine. In Fig. 3 the value for S has been plotted against T (Fraser *et al.*, 1953). It can be seen that, while there is reasonably good correlation for the non-toxic patients, there is a wide scatter in the toxic ranges, although the overall assessment of thyroid state is in good agreement. Of the 357 patients, 100 were thyrotoxic, 136 had non-toxic goitres, and 105 had no thyroid disorder, while 16 patients were clinically hypothyroid. The results in the first three classes are shown in Fig. 4.

This test has proved most useful in investigating the effects of drugs on thyroid function where several tests are often required on the one person (Greene and Farran, 1958; Greene *et al.*, 1958). In these circumstances ^{132}I is preferable to ^{131}I, because of its shorter half-life. Any residual activity due to ^{131}I contamination of the ^{132}I can be corrected for by subtracting the background counting rate before subsequent injections are given.

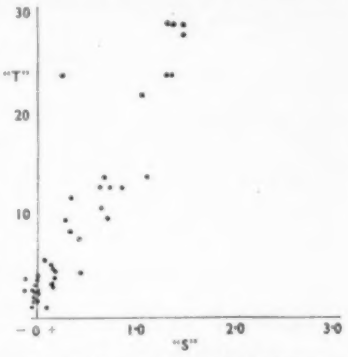

FIG. 3.—The relationship between S and T.

It is not possible to say whether or not S is of value in the diagnosis of hypothyroidism until more cases of proved hypothyroidism have been tested. Negative values of S probably indicate a hypothyroid state, but many more patients will have to be investigated before a firm conclusion can be reached regarding its suitability or otherwise for this purpose. A limited number of patients have been tested three months after having had treatment with radioactive iodine, but here again the results are inconclusive. It seems, however, that residual thyrotoxicosis can be excluded if S falls within the euthyroid range (0−0.8).

This test has now been in routine use at New End Hospital for over 18 months, and it is felt that its simplicity and the fact that an answer can be obtained less than an hour after requesting the test make it of considerable value in a busy department. It is merely a simplified version of other tests based on clearance rates, but, particularly if ^{132}I is used, it has the advantage that the radiation received from each test is practically negligible, which enables serial tests to be made safely on the same person over a long period.

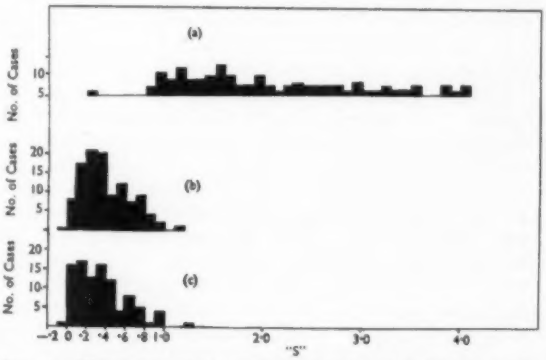

FIG. 4.—Histograms of the value of S obtained in (*a*) thyrotoxic patients, (*b*) patients having non-toxic goitres, and (*c*) patients without any apparent thyroid disorder.

Summary

A simple test for thyroid function which consists in measuring the rate of uptake of radioiodine by the thyroid during the first 30 minutes after the intravenous injection of 3–5 μc. of radioactive iodine is reported. A good separation between thyrotoxic and euthyroid subjects is obtained in about 90% of the cases tested.

Its main use is in serial measurements to test the response to drugs and other antithyroid substances. Other possible uses are discussed.

I wish to thank my clinical colleagues at New End Hospital for permission to use their material and also Miss E. V. Webb for her technical assistance.

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OCCULT BLOOD IN FAECES AFTER ADMINISTRATION OF ASPIRIN

BY

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It is known that aspirin (acetylsalicylic acid) may occasionally cause a gastric haemorrhage due to gastritis or a peptic ulcer (Douthwaite and Lintott, 1938; Hurst and Lintott, 1939; Hurst, 1943; Douthwaite, 1954; Muir and Cossar, 1955; Kelly, 1956; Lange, 1957). Despite the frequent use of this drug such complications have been rare. Moreover, it is difficult if not impossible—certainly in individual cases—to establish a direct proof of an immediate causal connexion. This may be a reason why insufficient thought has been given to this possibility.

In some of our patients, who had been treated with aspirin for rheumatoid arthritis, unexplained occult blood in the stools occurred. This article describes an attempt to determine the possible role of aspirin as a cause of this blood loss. The only paper on this subject was published by Lange in November, 1957, concomitantly with my thesis which recorded the results of our own investigation. Lange came to the conclusion that, even when the most readily soluble salicylic acid preparations were used, irritation to the gastric mucosa, accompanied by an occult loss of blood, could not be avoided. He was of the opinion that this irritation was of a general nature and was not confined to ultrasensitive persons. According to him the frequency of the occult loss of blood could be reduced if the patient took the medicine after meals. He furthermore suggested that the frequency of this blood loss might also be reduced if the tablets were given a good coating.

As Lange himself points out, his tests are open to criticism. He did not ascertain in all his test cases whether the occult loss of blood could not be due to some other cause than the taking of aspirin preparations. Furthermore, he did not prescribe a meat-free diet for his patients, and consequently there was always a possibility of the benzidine reaction in the faeces being influenced by the quantity of meat consumed by the patients prior to the tests. Lange accordingly found a relatively large number of instances in which there were positive benzidine reactions in the cases of patients who had not been treated with aspirin, whereas they should have been negative, provided that there was nothing else to cause bleeding. Moreover, he does not state the number of patients who had a positive benzidine reaction in the faeces, but only how many positive and negative specimens of faeces had been obtained from a group of patients during a certain period of time. It would have been more valuable if from each of the patients the same number of samples of faeces had been collected. During our tests we eliminated the above-mentioned drawbacks.

Method of Investigation

Since the results of tests for occult blood in the faeces are far from reliable in out-patients, the investigation was carried out only on patients who were hospitalized because of some rheumatic complaint. Those whose histories recorded stomach trouble were excluded from treatment with aspirin. Otherwise no selection was made.

The aspirin was administered in the form of tablets taken with milk or water shortly after a meal. As, according to the literature, a distribution of fine particles is less harmful than concentrated bulk, the patients included in this study were emphatically told not to swallow the tablets whole, but to permit them to disintegrate in the mouth or to chew them. It might have been better to administer the substance in the form of powder; but we gave up this idea, as patients generally object to taking it in this form and would seldom do so at home; it seemed to us that it would be better to carry out our experiments under conditions that were as near as possible to those generally prevailing in actual practice. We did, however, administer the drug in powder form to a small group of persons to determine whether results might be different.

The quantity of aspirin given as a medicine was not changed. In the main the quantity was 750 to 3,000 mg. a day, a few larger amounts being given as an exception. This moderate dosage may be taken as a criterion for the quantities generally administered in practice.

A meat-free diet was prescribed and the patient was not allowed to brush his teeth. In order to obviate possible disturbing factors, green vegetables and preparations containing iron were also forbidden; and, to preclude the possible influence of food consumed previously, no use was made of the first three lots of faeces produced after the diet had begun.

The benzidine reaction test was carried out as follows: Approximately 150 mg. of benzidine was dissolved in 7 ml. of ethyl alcohol 96%; to this was added 7 ml. of glacial acetic acid and 7 ml. of hydrogen peroxide. The strength of the resultant benzidine solution was therefore approximately 0.75%.

Gregersen (1919) showed that the benzidine reaction becomes more rapid in proportion to the concentration of the benzidine solution. He therefore recommended a solution with a strength of 0.5%, while Hulst (1933) obtained good results with a solution of 1%. We therefore certainly did not use too high a concentration of the solution in our experiment. This is proved by the fact that the reaction was always negative in the periods when no aspirin was taken. After the benzidine solution had been prepared we waited a while to make sure that it did not become coloured through the presence of impurities before the faeces were added. Then, using a glass rod, we took a small quantity of faeces from the centre of the mass and mixed it well with the benzidine solution. The following criteria were established:

Strongly positive ..	Deep blue colouring within 20 seconds
Positive	Deep blue colouring within 60 seconds
Slightly positive ..	Greenish blue colouring within 60 seconds
A trace positive ..	Green colouring within 60 seconds
Negative	No colouring within 60 seconds

In order to ensure the greatest possible uniformity in these observations all benzidine tests were carried out by the same technician.

Only after a positive or a negative reaction had been found in three successive specimens of faeces was the result

recorded as such. A benzidine reaction which showed only a trace (green colouring within 60 seconds) after aspirin had been taken was regarded as negative. As a rule the benzidine diet was prescribed after the patient had been taking aspirin for 14 days. In some cases, however, the diet was prescribed after the patients had been taking the medicine for a much longer period. A patient was said to react to aspirin *negatively* when the benzidine reaction was still not positive after aspirin had been taken for 20 days or longer (the last six days of the period with a diet).

A patient was said to react to aspirin *positively* when the benzidine reaction was positive during the taking of aspirin and became negative when he stopped taking it. The following scheme illustrates this classification.

Aspirin given { Benzidine − / Benzidine − / Benzidine − } Patient reacting negatively to aspirin.

Aspirin given { Benzidine + / Benzidine + / Benzidine + } Aspirin stopped { Benzidine − / Benzidine − / Benzidine − } patient reacting positively to aspirin.

As it was found that "entrosalyl" (coated sodium salicylate) never caused a positive benzidine reaction, those patients for whom salicyl therapy was desirable were given this medicine after they had stopped taking aspirin.

The results obtained when aspirin was taken were checked in two ways: (1) By determining the possibility of reproducing the phenomenon during alternating periods with and without administration of aspirin. Here the patient himself serves as a control. (2) By bringing groups of healthy volunteers into the scheme. With these control groups of healthy men and women we followed the same method of testing.

Results

Altogether 144 patients were examined. In four cases an alternating positive and negative benzidine reaction was observed after the patients had taken aspirin, and they could therefore not be designated as reacting positively or negatively. These four cases are left out of further consideration. Of the remaining 140, 95 showed a positive reaction to aspirin. These 140 patients comprised 38 males and 102 females; 23 and 72 respectively showed a positive reaction to aspirin (Table I).

TABLE I

	No.	Positively Reacting
Males	38	23 (60·5%)
Females	102	72 (70·6%)
Total	140	95 (67·9%)

Out of the 95 patients who had reacted positively, 79 who needed further treatment with salicyl were given sodium salicylate instead of aspirin (10 patients were given ordinary tablets and 69 coated tablets). In all these cases the benzidine reaction became negative.

Reproduction of the Phenomenon.—In 27 of the 28 cases in which the possibility of reproducing the phenomenon was examined, we were able to cause a repetition of the positive or negative benzidine reactions by administering or not administering aspirin. Examples are given in the Graph in which it is shown how the benzidine reaction repeatedly became positive after the administration of aspirin and negative when the drug was discontinued. In one case it was not possible to reproduce this condition. After this patient had taken aspirin for 18 months the benzidine reaction was strongly positive. When entrosalyl was substituted the reaction became negative. When aspirin was administered again the benzidine reaction was still negative after 45 days. It was not possible to ascertain the reaction of this patient again at a later date.

Controls with Groups of Healthy Volunteers

The possibility that rheumatic patients would react to aspirin differently from healthy persons should be considered. For this reason the same method of testing was applied to a number of men and women who could be assumed to be healthy. If a person was found to have any sort of gastric complaint he was excluded from the experiment.

It was found impossible to take an absolutely random sample from the general population. We had to confine ourselves to persons who took their meals in groups. This made it easier to check whether the diet prescribed was being strictly observed and also whether the tablets were taken as directed.

The control groups consisted of 20 women and 20 men (Table II). The doses prescribed for the 20 women were: 8 women to take 3 g. a day (3×2 tablets); 12 women to take 1.5 g. a day (3×1 tablet). It was our intention to split the group of men in the same way, but when a gastric ulcer was found in one of the women in the 3 g./day group it was decided for safety's sake not to give the dose again, although this isolated case may have been merely coincidental. Consequently each of the 20 men was given 1.5 g. a day.

TABLE II.—*Control Groups*

Quantity of Aspirin (mg. day)	Negatively Reacting	Positively Reacting			
		Total	Slightly Positive	Positive	Strongly Positive
		Females			
1,500	3	9	—	3	6
3,000	2	6	1	1	4
Total	5	15	1	4	10
		Males			
1,500	4	16	1	7	8

Table III shows a comparison between the results obtained with the control group and those obtained with the patients.

TABLE III

	No.		Positively Reacting	
	Females	Males	Females	Males
Control group ..	20	20	15 (75%)	16 (80%)
Patients	102	38	72 (70·6%)	23 (60·5%)
Total ..	122	58	87 (71·3%)	39 (67·2%)

If we now summarize the results of this experiment we find that after taking aspirin a large proportion of the persons examined (70%) had a positive benzidine reaction in the faeces (Table IV).

TABLE IV

	No.	Positively Reacting
Males	58	39 (67·2%)
Females	122	87 (71·3%)
Total	180	126 (70%)

Influence of Dosage

The quantity of aspirin given to the patients as a part of the medical treatment varied from 750 to 6,000 mg. a day. The customary doses were 1,500 and 3,000 mg. a day to 68 and 30 patients respectively. We did not find that a positive benzidine reaction occurred more often in those larger doses.

When the positive reactions were divided into slightly positive, positive, and strongly positive, we likewise found no distinctive difference between the results from larger or smaller doses.

No association was found between the ages of patients and their reaction to aspirin. The age of the patients was mostly between 40 and 60 years; there were a few younger and older patients—some of 11 and some of 72 years. On the whole, younger adults were taken for the control group.

As stated in the description of the method applied, the benzidine diet was as a rule prescribed after the patient had been taking asp.r.n for 14 days, and the first three lots of faeces were not examined.

In order to determine how rapidly the benzidine reaction can become positive we examined the stools of four patients from the very first day on which aspirin was taken. In these four cases the change from negative to positive occurred after three, six, four, and three days respectively (see Cases 1 and 2 in Graph).

Nevertheless the change need not always occur in such a short time. For instance, when we tried to reproduce the condition in a female patient who had originally reacted positively we found no clearly positive reaction even after three weeks of aspirin treatment. When the benzidine reaction was checked again after a space of 60 days it was found to be definitely positive (see Case 4 in Graph).

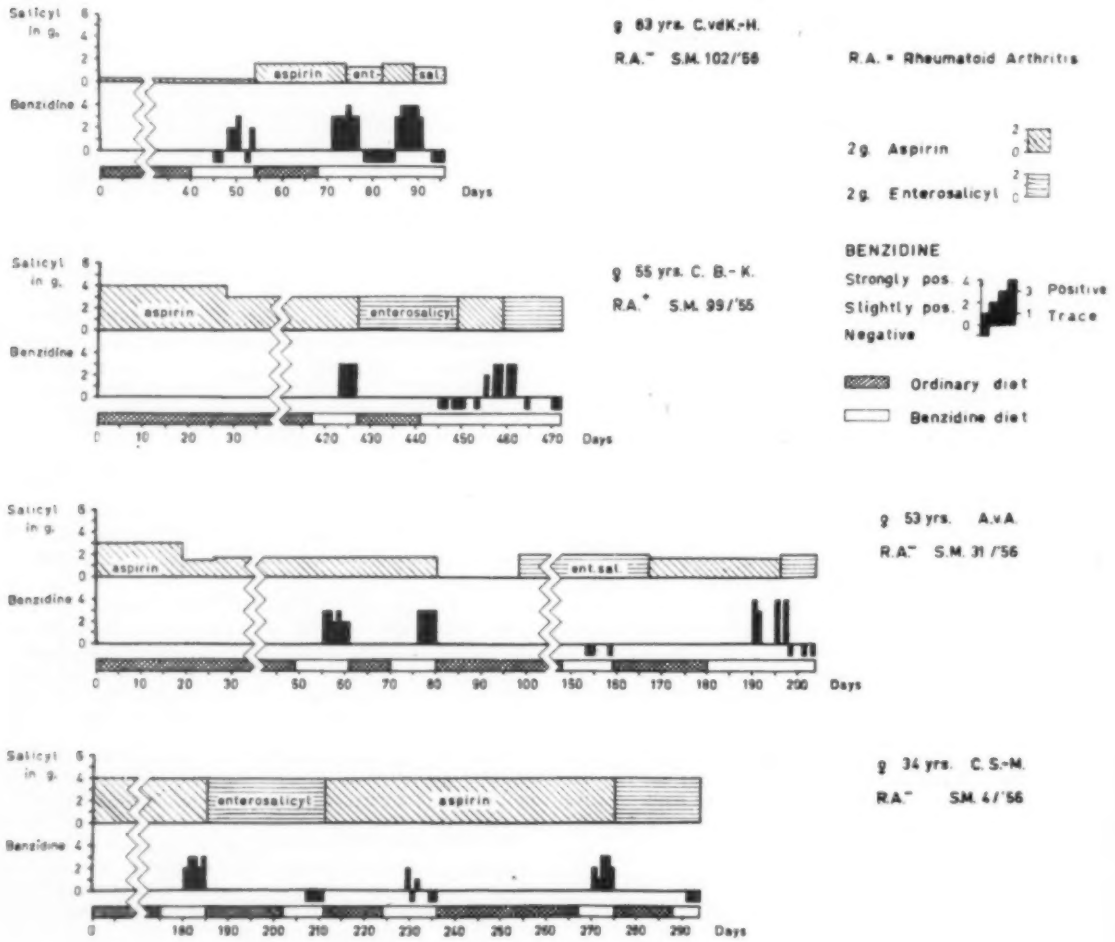
From the examples given it will be seen that among those persons who were recorded as having reacted negatively during our experiments there may have been some who would have shown a positive reaction during a longer period of observation.

In 70 cases we were able to determine in how many days the benzidine reaction became negative after the administration of aspirin was discontinued. The average period was found to be four to five days, but here again there were some exceptions. In three patients the benzidine reaction was still positive after 20, 23, and 31 days respectively. When the examination was repeated after 56, 43, and 53 days respectively the reaction had become negative.

It appears from our experiments that taking aspirin, even in moderate doses, causes a positive benzidine reaction in the faeces in a high percentage of cases.

It was not possible to find any association between the occurrence of this deviation and the occurrence of subjective complaints. Complaints of a slight feeling of fullness and "burn" in the region of the stomach were made by only a few of our patients. Such complaints were, however, made not only by patients who had reacted positively to aspirin but also by those who had shown a negative reaction. In the case of only one patient, to whom a dose of 3 g. of aspirin a day had been administered, the complaints were of such a nature that treatment had to be stopped. In the female control group, for whom 3 g. a day had been prescribed, complaints of stomach trouble were far more frequent than in the patients who had been given the same doses. Five of the 10 women undergoing the experiment complained of nausea and pains in the stomach. In two cases the pains were so violent that the women were unable to continue with the experiment. It is possible that the frequent occurrence of stomach trouble in this control group was due to a considerable extent to psychological factors. The persons concerned knew that they were undergoing a test, and they may have been expecting gastric troubles. On the other hand, the patients were given aspirin as a medicine, and it is therefore likely that although some of them were troubled they did not complain.

Some research workers have attributed stomach troubles when aspirin was administered to an increase in the value of the gastric acids. We did not carry out any systematic



experiments to determine the gastric acidity when aspirin was taken. As, however, we found five positive reacting patients with an achylia that was refractory to histamine, in addition to a few patients with an increase in gastric acid values after taking aspirin, it may be said that the increase in gastric acid values is possibly not the only factor when stomach troubles occur after the taking of the drug. It has been suggested in the literature that no stomach disorders occur when aspirin is administered as a powder. We have already said why we did not regularly give it in this form. We did, however, give a small control group of four patients and six healthy volunteers 500 mg. of aspirin powder suspended in water three times daily after meals. All these persons had previously shown a positive benzidine reaction after one tablet of 500 mg. had been taken three times a day. In all 10 cases there was once again a loss of blood found in the faeces. There was no clear difference in the strength of the reactions compared with those which occurred when tablets had been taken.

It would appear that the ideal substitute for the ordinary tablets would be coated tablets of aspirin, which would not disintegrate until they reached the small intestine. Talkov *et al.* (1950) do mention the disappearance of subjective disorders after patients had taken such tablets, but this does not imply that there was no occult loss of blood. We carried out a tentative experiment with coated tablets, which we gave to 20 patients who were showing a positive benzidine reaction caused by taking ordinary tablets. In 5 of these 20 cases the benzidine reaction became negative within four to seven days after taking the coated tablets. The reaction of two others became clearly less strongly positive, and in the 13 remaining cases the reaction after an average of 13 days was still unchanged in intensity.

From the data given in the literature it may be concluded that when aspirin is taken in moderation it is highly improbable that hypoprothrombinaemia is the cause of the gastric haemorrhage. Nevertheless, to ascertain whether this was the case four patients with strongly positive benzidine reactions during the administration of aspirin were analysed with regard to their coagulation mechanism. No disorder was found, and notably there was no hypoprothrombinaemia. Time and again normal values for the bleeding-time were found. Therefore in our opinion we need not take into account the possibility of a disorder in the coagulation mechanism of the blood being the cause of the positive benzidine reaction which we had found.

For various reasons we did not carry out a systematic *x*-ray examination whether or not there was an ulcer in these cases, especially as there were no complaints. The stomach and intestines were radiographed in only four cases in which the patients showed a positive reaction. There was no sign of disorder in any of these *x*-ray films that would account for the positive benzidine reaction. We did, however, prove by means of *x*-ray films the presence of a gastric ulcer in a woman in the control group who had been taking 3 g. of aspirin a day for a period of three weeks. This woman had never previously complained of stomach trouble. As she had violent pains coupled with a strongly positive benzidine reaction after taking aspirin we made an *x*-ray examination of the stomach. Unfortunately we did not have an *x*-ray film of her stomach taken before she had the aspirin. There is accordingly no proof that the gastric ulcer was brought about by the aspirin. It can be said with greater certainty that the aspirin was the cause of the stomach troubles and of the strongly positive benzidine reaction. For, after the medicine had not been taken for four days the stomach troubles ceased and the benzidine reaction became negative.

We considered the possibility of the positive benzidine reaction, after taking aspirin, being due to a substance other than blood. In order to preclude this possibility the stools of six patients were examined spectroscopically and spectrophotometrically. In cases with a positive benzidine reaction we found a typical blood-absorption curve. The experiment is explained at greater length elsewhere (Stubbé, 1957). Kelly (1956) has stated that the loss of blood as a consequence of the taking of aspirin may lead to serious anaemia. We on our part found a woman of 23 suffering from extreme anaemia (Hb content 30%), which had been brought about by taking not more than two tablets of 500 mg. of aspirin a day. In the hospital we found the benzidine reaction negative, as no more aspirin was administered after the patient was admitted. When we administered a tablet of 500 mg. of aspirin three times a day during two periods, after we had taken all kinds of precautionary measures, we found signs of melaena after four days and again after seven days, without any complaint on the part of the patient. No disorder could be found when the patient was suffering from melaena, either by *x*-ray examination or by coagulation tests; the bleeding-time was also normal. After iron had been administered orally it was found that the Hb content had risen to 90% within two months of taking aspirin. These extreme cases are, however, exceptions and are fortunately seldom met with. The occult loss of blood, on the other hand, is a complication very often encountered in aspirin therapy, as we have already said.

To obtain an idea of the amount of blood lost in such cases a few patients were given a small quantity of their own blood to drink 10 times a day. In this way we were able to ascertain with what loss of blood the criteria employed for determining the strength of the benzidine reaction approximately corresponds.* It was found that when 4 ml. of blood was administered there was a strongly positive benzidine reaction.

Although this experiment was carried out with only a few patients one might conclude from the results that a patient with a strongly positive reaction loses about 30 times 4 ml. = 120 ml. of blood a month. Those patients who show a strongly positive reaction within the space of a few seconds will probably lose even more blood.

By way of comparison we might take the average quantity of blood a woman loses a month during the menses. According to Wright (1952) the loss amounts to 40 ml. (varying from 10 to 210 ml.).

Discussion

It is known that bleeding may occur in the stomach after a person has taken aspirin. But, considering the enormous quantities of this drug which are consumed and the frequency with which it is taken, such an occurrence may be regarded as an exception.

Subjective complaints of the stomach are not of rare occurrence, but, so far as we know, no one has ever systematically tried to ascertain whether these coincide with organic disturbances. When there are no subjective complaints at all it is generally supposed that objective disorders are out of the question. From our experiments, however, it appeared that about 70% of the persons who took this medicine, and who mostly had no complaints, lost blood with the faeces. It goes without saying that the observance of a positive benzidine reaction is also dependent on the sensitivity of the reaction. The existence of a physiological blood content of the faeces was established in experiments by Hulst (1933) and others.

From this it would appear desirable not to raise the sensitivity of the reaction too high by making the concentration of the benzidine solution too strong. On the other hand, it is of interest clinically to be able to demonstrate the pathological loss of even small quantities of blood. As already stated, we used a benzidine solution of about 0.75% for our experiment, on the basis of data given in the literature. And it appears, from the fact that the reaction was invariably negative during the control periods without the administration of aspirin, that the reaction in the course of the experiment was not too sensitive.

The observations made by Douthwaite (1938, 1954) and other research workers, who with the aid of the gastroscope saw rapid changes occur in the mucous membranes only around the particles of aspirin and not at other places

*A detailed description of the method applied was given in our thesis (Stubbé, 1957).

on the mucous membranes, make it appear very likely that a direct local irritation of the gastric mucosa was the cause of the occult loss of blood. An allergic reaction to aspirin seems highly improbable in view of the frequent occurrence of the loss of blood and the absence of any other allergic symptom in any of the patients and control persons examined by us. It appears from the literature that the occurrence of hypothrombinaemia is very improbable when aspirin is taken in moderation. We could not find a disturbance in the coagulation mechanism during the loss of blood in any of the four cases in which we tried to establish this, and therefore the occult loss would also seem unlikely on this account. Furthermore, one should consider the possibility of increased capillary permeability, due to the taking of aspirin, accompanied or not by changes in the capillaries brought about by the sickness itself, being the cause of the occult loss of blood. In view of this possibility we are carrying out further experiments in this connexion. Provisional data on this subject make it improbable that the loss of blood can be due to capillary permeability of this kind. Although an increase in the gastric acid values during the taking of aspirin has been described by most writers, this does not imply that this increase is a causal factor where there is an occult loss of blood. And this is certainly not evidenced by the fact that we were able to demonstrate the occult loss of blood in five patients with an achylia refractory to histamine.

It has been demonstrated that the loss of blood may not always be ignored; this applies especially to the extent to which the patient is already anaemic and in a bad state generally. The taking of aspirin over a long period is most common in the case of persons suffering from rheumatoid arthritis. Many such patients are anaemic, a state which has also always been regarded as a consequence of the rheumatic process. Now that we know that aspirin can cause bleeding, it may be asked whether this has not likewise often played a more or less important part in bringing about anaemia.

As already stated, we gave patients who were suffering from a rheumatic complaint a coated sodium salicylate (entrosalyl), where we thought it necessary, instead of the aspirin. In none of these cases did we ever find a positive benzidine reaction. To 10 patients we gave ordinary sodium salicylate tablets—that is to say, not coated tablets. In these 10 cases also we did not find a single patient with a positive benzidine reaction. This therefore goes to show that the coating is not essential, as sodium salicylate apparently causes no irritation. The drawback of sodium salicylate, however, is that it has a weaker analgesic effect than aspirin. Moreover, when it is not coated it has a very disagreeable taste.

Thus the problem is to find a form for the aspirin which does not cause irritation of the mucous membranes. Consequently it is suggested, for instance, that the drug be given in powder form. But so far as the occurrence of occult bleeding is concerned we could not substantiate that the taking of powder as opposed to tablets made any difference in our examination of 10 patients.

Another possibility is the administration of aspirin in a coated form, in which case the tablet does not disintegrate until it reaches the intestine. Of the 20 patients examined by us after they had taken the coated form of tablet only five showed a negative benzidine reaction. It is not clear why the benzidine reaction was not negative in all 20 of the cases when we administered these tablets. We are not in a position to say whether any of the tablets were imperfectly coated or not. Even with a good coating there is, however, the possibility of occult loss of blood due to irritation of the intestinal mucosa, about which nothing is known.

Conclusions

From the experiments described above it appears that there is a very frequent loss of blood with the stools. The amount of aspirin administered has no evident influence on the occurrence and the seriousness of the disorders. The administration of aspirin in powder form suspended in water produces the same results as those obtained when tablets are given. Although it has not been definitely established in what way the occult loss of blood is caused when aspirin is taken, our experiments, following on the information already available, tend to show that a local irritating effect on the gastric mucosa is most probable. When patients are treated for a long time with aspirin it is advisable that there be a regular check of the benzidine reaction in the faeces. If the reaction is found to be strongly positive a discontinuance of this treatment seems to be indicated.

When occult blood is found in the faeces without known cause it is necessary, in the first place, to preclude the possibility that this might be occasioned by aspirin before carrying out an extensive analysis with, among other things, a complete *x*-ray examination. We must also consider aspirin as being the possible causal factor (as in one of our own cases) when a case of serious anaemia occurs in which a negative benzidine reaction can be found due to the discontinuance of the drug.

Summary

Occult loss of blood in the faeces was proved to occur in about 70% of the 180 persons to whom aspirin in the form of tablets had been administered. The details of the conditions of this study and the criteria applied have been given. Results obtained with the 140 patients treated with aspirin in the wards of the rheumatology department were entirely comparable to those found in the control groups, consisting of 40 healthy volunteers.

It was possible to prove conclusively that aspirin was the cause of this loss of blood, as this phenomenon appeared to be reproducible. The quantity of aspirin administered did not have a great influence on the occurrence and the seriousness of the disorder. The most common doses were 1,500 mg. and 3,000 mg. a day. Identical results were obtained when aspirin in powder form suspended in water was administered to a small group and when the same persons were given tablets. Finally, the results obtained when coated tablets of aspirin were administered are recorded.

It was possible to demonstrate spectroscopically and spectrophotometrically that a positive benzidine reaction after the taking of aspirin is indeed due to the presence of blood. In a number of cases it was shown on the basis of the strength of the benzidine reaction that the quantity of blood lost when aspirin was taken may not always be ignored.

These experiments were carried out in the Rheumatological Department "Sole Mio" at Noordwijk and in the Department for Rheumatology and Internal Medicine of the University Hospital at Leyden. I am grateful to the nurses who by their loyal cooperation made these experiments possible, and to those volunteers who came forward to form the necessary control groups. To Miss C. van Heulen, technician in Noordwijk, I am extremely indebted for the manner in which she collaborated in carrying out the tests. The interest and practical assistance of Miss J. H. Pietersen, rheumatologist in Noordwijk, constituted valuable support in the course of these studies.

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USE OF IPRONIAZID IN ISCHAEMIC ANGINA PECTORIS

BY

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Iproniazid ("marsilid"; 1-*iso*nicotinyl-2-*iso*propylhydrazine phosphate), a derivative of isoniazid, was found by Cesarman (1957) to relieve angina pectoris in a patient who was given the drug for its effect on mood. Cesarman followed up this observation in 40 patients with angina pectoris and showed that iproniazid reduced the frequency and severity of their attacks.

We have carried out a preliminary trial with iproniazid in 40 patients with angina to evaluate its effectiveness, to investigate its mode of action, and to assess its place in treatment.

Method

All 40 patients had frequent angina pectoris. Most had pain on slight effort such as walking a few steps, and some had rest pain also. In 24 patients the situation was deteriorating and in 16 it was static. In all but five the electrocardiogram showed changes of previous cardiac infarction or present coronary insufficiency. All patients received other routine treatment such as bed rest, anticoagulants, and trinitrin, if those seemed to be indicated. Long-acting nitrites were not given. Iproniazid was prescribed in doses of 50 mg. two or three times daily.

Results

Patients began to improve five days to one month after starting treatment, the average period being about two weeks. After one month of treatment 17 patients had pain only occasionally, and much greater effort was required to provoke it. A further 14 patients were improved but still had angina on moderate effort. Of the remaining nine patients, one has died, four were unchanged, and four had stopped the drug after a week or two because of side-effects. Nineteen patients have been followed for three months or more and the improvement has been maintained in all but two.

After one month the electrocardiogram was improved in 9 patients, unchanged in 19, and worse in 5. Of the patients followed for three months or more the electrocardiogram improved in the majority, but was unchanged in four and worse in two. Two patients with the changes of coronary insufficiency, which were reversible with trinitrin, became free of pain despite the persistence of these changes.

Side-effects

Side-effects occurred in most patients after one to four weeks of treatment. The commonest was giddiness (lightheadedness), which was present in 15 patients. Usually it was mild and temporary, but in five patients it was severe, and the drug had to be stopped. Two of these patients fainted. Syncope was associated with a fall in blood pressure and was presumably vasomotor rather than cerebral in nature. In one patient who complained of dizziness the blood pressure fell from 200/110 to 110/70 while on iproniazid. In the whole series the average fall in systolic pressure was 15 mm. Hg. Impotence was common amongst the men, but was not resented by elderly patients.

A rapid increase in weight of the order of 14 lb. (6.4 kg.) in a month occurred in four patients, and was associated with a voracious appetite in two of them, but not in the other two. In the majority of patients, however, there was little or no gain in weight.

Greater confidence, a lightening of mood, or frank euphoria was the rule in patients treated with iproniazid, and proved a therapeutic ally, tending to prevent patients taking a pessimistic view of other side-effects.

Three patients complained of twitching of the limbs, two of weakness in the legs, three of constipation, and two of frequency of micturition. Ankle oedema with a rise in jugular venous pressure appeared in two patients, but cleared rapidly when the drug was withdrawn and did not return on restarting it. Two patients complained of breathlessness and showed pulmonary oedema and Kerley lines on *x*-ray examination. There was no triple rhythm or change in heart size. The lung changes cleared in one patient within 10 days of stopping iproniazid, without other treatment. The other patient received mercurial diuretics in addition, but remained well when these were withheld.

In two patients in whom iproniazid was stopped after a short period, the pain returned in about 10 days. Isoniazid was substituted in one patient and was found to be ineffective. Two patients, one with severe giddiness and one with peripheral oedema, insisted on restarting iproniazid because while on the drug they were free from pain for the first time in several months.

In an editorial (1958) liver damage has been reported in patients receiving iproniazid. Ten of our patients were receiving anticoagulants, which interfere with the hepatic synthesis of prothrombin, when treatment with iproniazid was started. The drug did not produce increased sensitivity to the anticoagulants. No evidence of hepatic disorder was detected in any of our cases, but liver-function tests were not carried out routinely.

Discussion

In this preliminary study we decided to dispense with a control series because of the powerful effect of iproniazid on anginal pain reported by Cesarman (1957) and Cossio (1957, 1958). We consider that this decision has been amply justified and confirm that the drug relieves angina pectoris. It is much more effective in this respect than the long-acting nitrites. Its action cannot be accounted for by the euphoria it sometimes produces. It may relieve pain although the electrocardiogram deteriorates. In this small series of patients with crippling angina pectoris relieved by iproniazid, the serial electrocardiographic findings and mortality rate were such as might be expected from routine treatment alone; there was no evidence that iproniazid influenced the natural history of the disease. On the basis of similar observations Cossio suggests that the drug acts by a selective analgesic action on muscle pain of ischaemic origin. It has since been shown to relieve pain in certain cases of carcinomatosis and rheumatoid arthritis, and it may be that the drug acts by blocking pain in the central nervous system. Its most powerful known pharmacological action is the blocking of monoamine oxidase activity, and it is thought that some or all of the observed clinical effects may be due to this.

Undue exertion may precipitate cardiac infarction in patients with coronary artery disease (Yater *et al.*, 1948). Iproniazid, by blocking warning pain, may increase the risk of infarction, and anticoagulant protection is theoretically desirable for patients on iproniazid.

Severe and recurrent anginal attacks frighten, depress, and exhaust the patient and presumably lower the threshold for pain. Iproniazid can help dramatically by its pain-blocking and euphoriant actions, and there is a real place for it in the treatment of such patients. It should be continued for two or three months or until the electrocardiographic changes of coronary insufficiency, if present, have resolved. The drug can then be withdrawn in order to assess the

situation on the basis of the number of anginal attacks and the effort required to produce them. It should always be stopped before the patient returns to work.

Because of the danger of masking myocardial ischaemia, the numerous side-effects, and the risk of serious liver damage, iproniazid is not indicated for the patient with mild angina.

Although the drug could theoretically give rise to "silent infarction," this did not happen in any of our patients. Two of them had infarcts while receiving iproniazid. Both were at rest at the time and had typical pain.

The side-effects of iproniazid are described by Robitzek and Selikoff (1952) as, firstly, those referable to autonomic stimulation, including dryness of the mouth, constipation, delayed micturition, and difficulties in visual accommodation; secondly, those referable to central nervous system stimulation, including vertigo, muscle-twitching, hyperreflexia, excitement, euphoria, somnolence; and, thirdly, those referable to antagonism to vitamin B, including peripheral neuropathy. Unfortunately these and other side-effects limit the usefulness of the drug.

Summary

Iproniazid has been given to 40 patients with severe angina pectoris from occlusive coronary atherosclerosis, and was highly effective in reducing the frequency and severity of anginal attacks. It appears to act by blocking pain and not by improving the coronary circulation. Side-effects are common; many of our patients complained of giddiness and two developed pulmonary oedema, presumably from fluid retention. The blocking of angina may encourage the patient to be more active and may precipitate infarction. Because of this and the side-effects, the drug is not indicated for patients with mild angina pectoris. In the patient with severe and intractable angina it is of great value, especially if anticoagulant therapy can be given in addition. The patient can often be helped over a prolonged ischaemic episode, the drug being withdrawn when the condition improves.

We are grateful to Dr. Margaret Briggs, of Roche Products Limited, for her help and for supplies of marsilid.

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"We have learnt a great deal during the last three years from three reactor accidents which have led to partial melt-out of the reactor fuel elements. Although two of the reactors were put out of commission for a year and one was written off, no one was hurt by these accidents or received an overdose of radiation. The results of the accidents agree in a remarkable way with laboratory experimental work in showing that only a very small fraction of some of the bone-seeking isotopes escaped from the melted fuel. The disturbances due to these accidents were accordingly less than envisaged previously. Later generations of reactors than these early models are much better protected by containment and instrumentation, and some papers have shown considerable progress in advanced designs of containment which are thought to be proof against the maximum credible accident. This gives us considerable confidence in safe operations in the future, and we may, in due course, expect the location of plants in more populated areas. There has also been a growth of national reactor safety and inspection organizations, analogous to those in being for the aircraft industry. They inspect designs and prescribe codes of operation to help to maintain safety."—From a lecture by Sir JOHN COCKCROFT, F.R.S., to the Danish Society of Civil Engineers on October 6.

JAUNDICE ASSOCIATED WITH ADMINISTRATION OF IPRONIAZID

REPORT OF TWO CASES

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Iproniazid ("marsilid"; or 1-*iso*nicotinyl-2-*iso*propylhydrazine phosphate) is a variant of isoniazid, which was first used for its antituberculous properties in 1952. Then described as a drug which made patients "dance and sing in the ward" and as a "fountain of energy," it was discarded by chest physicians as too apt to produce side-effects, including psychotic episodes; it has since been hailed by psychiatrists as a powerful "energizer," and been found useful in the treatment not only of depressive states but also in angina pectoris and collagen diseases, gastro-intestinal conditions, etc. Zeller *et al.* (1952) found that iproniazid was a powerful inhibitor of amine oxidase. Udenfriend *et al.* (1957) were able to demonstrate a rapid and large rise in brain serotonin in animals given the drug. The effect of the drug on mood in humans has been attributed to this increase in serotonin.

In a symposium (1958) in New York in 1957 many preliminary studies were presented, but concluding speakers stressed the need for carefully controlled trials before definite claims for the value of the drug in psychiatric and other conditions could be made. During the course of such a trial in this hospital, two cases of jaundice have occurred. The possibility of this drug being hepatotoxic has recently been raised. In view of the increasing use of iproniazid in psychiatric practice, these cases seem worthy of immediate report.

Case 1

The patient, a 53-year-old working-class widow, had been subject to spells of agitation and depression, with increasing suspiciousness and misinterpretation for three years. She was previously hardworking and loyal, and had struggled to bring up five children, one of whom was diabetic from infancy. She had had no serious illness previously, and had never been jaundiced. She had not received injections and there was no contact with cases of infective hepatitis.

She was admitted to hospital on October 11, 1957, and made a good initial response to hospitalization. Iproniazid was first given at 150 mg. daily on January 11, 1958, and reduced to 100 mg. daily on February 11. During the first week of March she began to feel vaguely unwell, suffered from giddiness and palpitations, and later complained of superficial pains in the limbs and shivering attacks. All but the latter symptoms have been described as side-effects and are often encountered in iproniazid therapy. Our patient minimized these for fear that she might be taken off the drug, which was helping her considerably. On March 24, however, she developed mild anorexia with constipation and took to her bed. Iproniazid was discontinued. Two days later, though subjectively much improved, she was jaundiced and had a pale stool and biliuria.

On examination the liver edge, slightly tender, could be palpated two fingerbreadths below the costal margin, but liver dullness was not greatly increased. She was, and remained, apyrexial. (For details of investigations, see Table.) With a low-fat diet, rest, and vitamins her strength and

appetite improved further, though jaundice deepened. On April 6, however, there was a return of anorexia and nausea was persistent. Her clinical condition deteriorated, some petechiae appeared, hepatomegaly was no longer demonstrable, but the spleen was found to be enlarged and easily palpable. Rubefacience, circumoral pallor, with "cherry-red" lips and red palms, were observed. There was no tremor or other signs of encephalopathy. Subacute hepatic necrosis was diagnosed, and our findings were confirmed by Dr. Philip Harvey, who kindly saw the patient and on April 9 arranged her transfer to St. Stephen's Hospital for further investigation and treatment.

Intravenous corticotrophin in dextrose was immediately given, the patient receiving a total of 600 units over a period of three days. Diet was restricted to 1,500 calories (with 35 g. of protein). Neomycin and tetracycline were given orally, together with soluble insulin (5 units before meals) and propyltestosterone, these measures aiming at diminishing protein katabolism. Vitamin K, folic acid, and vitamin B_{12} completed the regime. Twelve hours after initiation of this therapy icterus had greatly diminished. The serum bilirubin level had fallen from 16.6 to 6.4 mg. at the end of corticotrophin administration; by April 25 this level had fallen to 2.8 mg., and her recovery has since been uninterrupted.

A liver biopsy, performed by Dr. Gordon Signy on April 14 (after completion of the corticotrophin treatment), was reported as follows: "There are widespread fatty changes. There are focal areas of swollen hepatic cells and some bile thrombi, focal areas of infiltration, with small cells, including lymphocytes, polymorphs, and eosinophils, mostly occurring round the central vein. There is some increase of collagen fibres around the central vein and the portal spaces. The picture is one of focal necrosis." An electrocardiogram showed sinus bradycardia only. The white blood count remained within normal limits, and the sedimentation rate was not raised.

Case 2

A 31-year-old single woman, secretary to a business executive, had been admitted for the third time to Bethlem Royal Hospital in September, 1957, on account of severe and disabling neurotic symptoms accompanied by depressive features. After discharge from hospital in January, 1958, she remained apathetic, mildly depressed, and unable to work.

Iproniazid was given on January 31 in doses of 150 mg. daily and continued until April 12. Soon after initiation of this therapy she was able to resume work, and remained so well that she failed to keep her out-patient appointments. At the beginning of May she began to feel ill, nauseated, tense, and depressed, but attributed such symptoms to her anxiety relating to a difficult emotional situation. Nausea had been a frequent feature of her various neurotic illnesses.

When seen in the out-patient department on May 9 she appeared agitated and depressed. Iproniazid was again prescribed in doses of 75 mg. daily, combined with chlorpromazine, 150 mg. daily. Later that day she noticed that her urine was dark and her stools were pale. On the following day jaundice appeared. Iproniazid and chlorpromazine were discontinued after only a few doses. When she reported sick to her firm's medical officer she was found to be pyrexial, and on examination the liver was palpable and tender. "Toxic jaundice" was diagnosed, and she was sent home to bed and treated with a fat-free diet. She had not received injections and there was no contact with other cases of jaundice. Unfortunately, we were not informed of these events until May 30, by which time the jaundice was resolving. She was visited at her home on June 1. On examination she was still slightly jaundiced, the liver edge was palpable but not tender, there was no splenomegaly, and haemorrhage and other skin manifestations were absent. After this visit she was admitted to St. Stephen's Hospital, and a liver biopsy was carried out by Dr. Gordon Signy on June 6. The tissue obtained proved to be part of a haemangioma, and no information could be obtained from the few liver cells present in the sections. The patient suffered no after-effects and was discharged home.

Laboratory Investigations on June 1.—Serum bilirubin: direct, positive; indirect, 2.3 mg.; thymol turbidity, 3 units; zinc flocculation, 9 units; colloidal gold, 0; alkaline phosphatases, 9.6 units; serum transaminase, 47 units; Total protein, 6.5 g. (albumin 4.2 g., globulin 2.3 g.). Electrophoresis showed that the α_2 pattern was less prominent than usual. Abnormality of gamma-globulin was not found.

Discussion

Jaundice was reported during iproniazid administration in tuberculous patients (Bosworth *et al.*, 1955; Ogilvie, 1955). Although only one more case has been published since then (deVerteuil and Lehmann, 1958), jaundice was referred to by Kline (1958) as the most serious complication of iproniazid treatment. The incidence of this jaundice is estimated to be under 0.05% and to approximate that of infective hepatitis (Marks, personal communication). The mortality rate, however, is higher than that reported in infective hepatitis.

The five cases reported during treatment of tuberculosis recovered, but the case reported by deVerteuil and Lehmann, occurring during a trial of iproniazid on 31 depressed and apathetic patients, was fatal. Necropsy in this case showed a "hepatic necrosis of the type sometimes seen in response to toxic agents."

Scherbel (1957a) has described four cases of jaundice in a trial of isoniazid and iproniazid in rheumatic arthritis. In two of his patients there was evidence of previous liver damage: one patient was alcoholic and had a portal cirrhosis and the other, previously subjected to cholecystectomy, had a biliary cirrhosis. The liver biopsies presented a picture typical of "viral hepatitis." The serum bilirubin was 7.2 mg. in the most severe of his cases. Unfortunately, it is not clear from his report whether the patients were receiving isoniazid or iproniazid when jaundice occurred.

During the course of the above clinical trial Scherbel (1957b) described a state of behavioural hyperactivity in some of his patients who were receiving iproniazid. Labora-

Table of Laboratory Investigations

	March 26	April 2	April 11	April 14	April 25	May 6	May 24
Bilirubin	4·2 mg.	19·4 mg.	16·6 mg.	6·4 mg.	2·8 mg.	1·4 mg.	0·6 mg.
Alkaline phosphatases	18·8 u.	19 u.	26·7 u.	—	—	7 u.	—
Thymol turbidity	6 u.	3 ,,	2 u.	—	—	3 ,,	—
Thymol flocculation	Neg.	Neg.	Neg.	—	—	Neg.	—
Zinc turbidity	7 u.	6 u.	6 u.	—	—	3 u.	—
Colloidal gold	—	—	—	Neg.	—	—	—
Total protein	6·1 g.	7·1 g.	—	—	—	7·4 g.	8·6 g.
Albumin	3·8 ,,	3·6 ,,	—	—	—	3·9 ,,	5·9 ,,
Globulin	2·3 ,,	3·5 ,,	—	—	—	3·5 ,,	2·7 ,,
Serum transaminase	—	—	160 u. ml.	—	—	—	—
Prothrombin time	—	—	—	19 sec. (14 sec. control)	—	—	—
Blood urea	—	—	—	29 mg.	—	—	—
Haemoglobin	10·9 g.	—	—	12·7 g.	—	12·7 g.	—
Urine	Urobilin + Urobilinogen—not detected	—	Bile—trace Urobilin—excess Urobilinogen—excess	—	Urobilin—trace Urobilinogen—not detected		

tory investigations showed an increase in gamma-globulin, a decreased pseudo-cholinesterase, and increased bromsulphthalein retention in the absence of a rise in serum bilirubin. These findings were suggestive of hepatic dysfunction.

Pare (personal communication) has studied the effect of iproniazid on the serum transaminase level and found this to be increased in some patients, although other liver-function tests remained normal. This again might suggest some liver dysfunction.

Further evidence of liver involvement is supplied by Fouts and Brodie (1956). These authors discovered that iproniazid inhibited the enzymes in the liver, whose function is to detoxify such drugs as barbiturates, amphetamine, aminopyrine, and acetanilid. Toxic cerebral reactions following injections of pethidine have been reported by Mitchell (1955) and by Papp and Benaim (1958), and can be similarly explained on the basis of potentiation of the drug by iproniazid.

Randall (1958) reports slight parenchymatous degeneration in the liver and kidney, engorgement of the spleen, and bone-marrow hyperplasia in animals receiving large doses of iproniazid. Such changes were dependent on the dosage administered, and all were reversible.

Our two cases of jaundice occurred during a clinical trial of iproniazid on 60 depressed patients. Case 1 had received the drug for 72 days to a total of 8.6 g. when jaundice developed. The course of the disease was unlike that of infective hepatitis. Prodromal symptoms were minimal, asthenia and anorexia becoming marked only when clinical signs of necrosis supervened. Liver enlargement and tenderness were slight. There was no fever, and the E.S.R. remained normal throughout her illness. The initial liver-function tests were in favour of intrahepatic cholestasis. In common with other investigators, we found disturbance of protein metabolism with an increase in globulin. Unfortunately, electrophoretic studies were not carried out. The marked change in condition on the twelfth day of jaundice, with the development of clinical signs of liver failure, pointed to the onset of necrosis. This diagnosis was supported by a high serum transaminase level and by the biopsy findings, which showed evidence of focal necrosis in spite of the administration of corticotrophin for three days beforehand. Moreover, the presence of eosinophilia in the sections is strong evidence of drug-induced jaundice (Hollister, 1957).

Case 2 had received iproniazid for 75 days to a total of 11.25 g. It is unfortunate that the case was not seen until 22 days after the onset of jaundice, by which time she was recovering. No definite conclusions can be reached on the information available.

The hypothesis was originally put forward that jaundice occurring in iproniazid therapy was due to a coincidental occurrence of viral hepatitis and an inhibition of the amine oxidase system by the drug, causing failure of the detoxicating mechanisms of the liver. From the evidence available, however, it is difficult to escape the conclusion that iproniazid may have a direct toxic effect on the liver. The fact that jaundice has occurred in patients receiving as little as 25 mg. daily and that it appears unrelated to the duration of administration (Marks, personal communication) suggests that an element of idiosyncrasy may be present.

While it is difficult to decide at this stage whether iproniazid jaundice is of obstructive or hepatocellular type, the severity of some of the cases reported, including our first case, supports the latter possibility. Moreover, our liver biopsy provided definite evidence of hepatocellular damage. The picture was very different from that encountered in chlorpromazine jaundice, obstructive in type and benign in course, in which one invariably finds bile plugs in biliary canaliculi and minimal inflammatory changes (Movitt *et al.*, 1955).

It is clear that further research is needed to establish beyond doubt the mechanisms whereby iproniazid produces liver damage and jaundice. It is hoped that such risks can be eliminated and that this very helpful drug can continue to be used by psychiatrists and physicians with a greater degree of safety.

Summary

Two cases of jaundice occurring during a clinical trial of iproniazid in 60 depressed patients are reported. Both patients recovered.

Details of biochemical investigations and of a liver biopsy are given. These, together with the course of the disease, suggest that iproniazid is a hepatotoxic drug. Possible mechanisms of action are discussed and the need for further research is emphasized.

We thank Dr. R. F. Hobson and Dr. J. G. Hamilton, under whose care the patients were admitted, for permission to publish this report, and Dr. Linford Rees for his advice and encouragement. To Dr. Philip Harvey we are indebted for seeing and treating our patients; and to Dr. Gordon Signy for performing the liver biopsies. Dr. J. Marks, of Roche Products Ltd., supplied the marsilid for our clinical investigation and provided us with much unpublished information.

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TOXIC EFFECTS OF IPRONIAZID IN A PATIENT WITH ANGINA

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Iproniazid (" marsilid "), closely resembling isoniazid in its chemical structure, was originally planned as an antituberculosis drug. Its use in tuberculosis had to be abandoned because of its unpredictable side-effects on mood, ranging from mental excitement to frank psychoses, when given in doses of 4 mg. per kg. of body weight (200–300 mg. a day) as at first advised (O'Connor, Howlett, and Wagner, 1953). This euphoric effect was recently exploited in psychiatry for the treatment of mental depression, where, with smaller doses (100–150 mg. a day), promising results were obtained (Kline, 1958; Dally, 1958). The use of iproniazid in angina pectoris is based on a chance observation in a patient with mental depression who recovered from incapacitating angina while on the drug. Encouraged by this result, Cesarman (1958) tried iproniazid in 41 patients with moderate to severe angina. He reports " total remission " of anginal pain in all of his patients, with electrocardiographic improvement in some. Cossio (1958) out

of 36 patients found almost complete relief of angina in 15, improvement in 11, and no benefit in 10. The daily dose varied from 100 to 150 mg. (two to three tablets). Side-effects have been minor, such as euphoria, constipation, difficulty of micturition, giddiness caused by orthostatic hypotension, and impotence. Dally in his recent large series of 131 psychiatric patients mentions only two in whom treatment had to be stopped on account of fainting caused by postural hypotension.

We were less fortunate in one patient, out of the few, in whom the drug was given for incapacitating decubital angina by one of us (C. P.). This patient developed a transitory toxic cerebral state while taking iproniazid.

Case Report

A married woman underwent bilateral lumbo-dorsal sympathectomy for severe hereditary hypertension in 1948, when aged 40. There was at the time slight renal involvement and grade II–III retinopathy; but the main indication for operation was disabling angina with attacks refractory to nitrites, lasting for hours, cut short only by injections of morphine. She did not sustain cardiac infarction then or at any time later, and the electrocardiogram showed extreme left ventricular strain with ischaemic changes only. Surgery proved a great success; she was able to resume an active life, lost the angina, and the electrocardiogram reverted to normal. Now, ten years after the operation, the blood pressure in erect posture is still normal, while in recumbency it varies between 160/100 and 180/120.

During the past four years the cardiac symptoms recurred in the form of increasingly severe decubital angina. It was thought that the raised blood pressure in the lying position was causing the attacks, during which the electrocardiogram showed acute ischaemic changes. Prolonged bed rest with ganglion-blocking agents and rauwolfia, which effectively lowered the recumbent blood pressure, did not prevent the attacks. Heavy sedation, long-acting nitrites, and various coronary vasodilators were all tried without success. Parenteral pethidine, 100 mg. at first, later 200 mg., suppressed attacks of moderate severity; occasionally she needed morphine in addition. Pethidine never caused any side-effects, and the morning after the injections she was as usual active in her home. In March, 1958, when she had almost daily attacks, left stellate ganglionectomy was performed. After a fortnight the attacks reappeared and within days they became as severe as they were before the operation.

Iproniazid was started on April 26. For the first fortnight she was given 50 mg. twice a day, then three times a day. After a fortnight the attacks became less frequent—about twice weekly, and milder. Trinitrine was effective for the lighter attacks, though for the severe ones she still required pethidine injections. At this stage the only adverse iproniazid effect was pronounced postural hypotension. On May 27 she complained of difficulty of micturition. At 10 p.m. on May 30, after not having had angina for four days, she had a severe attack. Pethidine, 100 mg. by injection, did not relieve her, and the same dose was repeated half an hour later. Within minutes she became extremely restless and confused, and passed into a state of uncontrollable hyperactivity. She was tossing and turning, flopping her arms aimlessly, and it was difficult to keep her in bed. There was general clonus, tremor, excitation, grinding of teeth, and continuous picking of bedclothes. She was semiconscious, had an anxious expression, and became completely unmanageable.

Paraldehyde, 5 ml., phenobarbitone sodium, 3 gr. (0.2 g.), and promethazine hydrochloride, 50 mg. by injection, and pentobarbitone sodium and quinalbarbitone sodium, 3 gr. (0.2 g.) of each orally, were given with no effect. Finally chlorpromazine, 50 mg. by injection, two hours after the attack began, quieted her, and she fell asleep within half an hour. Iproniazid was now stopped, she having had a total of 4,400 mg. in 35 days. Next day she was calm and in a normal mental state; she had impaired memory of the events of the previous night. The next evening (June 1) she had a further bout of angina, suppressed with 200 mg. of pethidine by injection. Again a similar state of agitated hyperactivity developed, which was easily controlled with an injection of 50 mg. of chlorpromazine. Thereafter oral chlorpromazine was given, 50 mg. three times a day. A further attack of angina on June 3, for which 200 mg. of pethidine had to be injected, was not followed by restlessness. One week after iproniazid had been stopped postural hypotension and difficulty of micturition still persisted.

Liver-function Tests.—Serum bilirubin: direct, negative; indirect, 1 mg. per 100 ml.; thymol turbidity, 3 units; zinc flocculation, 9 units; colloidal gold, 0; alkaline phosphatase, 3.9 units; serum transaminase, 30 units per ml. Serum proteins: total, 5.8 g. per 100 ml. (albumin 4 g., globulin 1.8 g.). Electrophoresis of proteins showed no rise of γ-globulin. Urine analysis showed no abnormalities.

Discussion

In a recent symposium on the biochemical and clinical aspects of iproniazid Kline (1958) reported that jaundice was the most serious side-effect of the drug. One of us (S. B.) has studied two cases of iproniazid jaundice; his findings are reported at p. 1068. Hepatic dysfunction in the absence of jaundice has been reported by Scherbel (1958) in the treatment with this drug of patients suffering from rheumatoid arthritis. Four of his cases suddenly developed restlessness and hyperactivity. Laboratory investigations showed an increase in bromsulphthalein retention, a diminution of pseudo-cholinesterase, and a disturbance of proteins with an increase of γ-globulin.

Fouts and Brodie (1956) found that iproniazid inhibits the enzyme system in the liver responsible for detoxication of various drugs—for example, barbiturates, amphetamine, aminopyrine, and acetanilid. This study, together with that of Randall (1958), explains the potentiation of these drugs by iproniazid. He also suggests that the toxicity of iproniazid may result from this enzyme inhibition.

Pethidine is de-esterified and demethylated in the liver (Goodman and Gilman, 1955), and it is now recommended that this drug should not be used in patients suffering from severe liver disease, as exaggerated responses, especially cerebral excitation and confusion, may occur (Dundee and Tinckler, 1952).

There was a clear temporal relationship in our patient between the administration of pethidine and each attack of cerebral excitement. Since pethidine was given in therapeutic doses, such exaggerated response could be interpreted as evidence of interference by iproniazid with the detoxicating mechanism of the liver. Such liver-function tests as were carried out were normal. It is unfortunate, however, that no test of bromsulphthalein retention was performed in our patient, since this is one of the most sensitive tests available (Neefe *et al.*, 1955).

Randall has shown that iproniazid has a cumulative effect, and this may explain why our patient, who was receiving pethidine frequently, developed signs of central nervous system intoxication only during the fifth week of iproniazid treatment. The slow excretion of iproniazid accounts for the persistence of the ganglion-blocking effect as well as the exaggerated response to pethidine after its withdrawal.

Among the many reports dealing with the toxic effects of iproniazid upon the central nervous system, we found only one other instance where the first signs of toxicity appeared after pethidine (Mitchell, 1955). A patient with tuberculosis who had been taking 250 mg. of iproniazid a day for one month developed nausea and muscle-twitchings 20 minutes after 100 mg. of pethidine, which he used to take without side-effects. He became cyanosed, was sweating, and had a rapid pulse, exaggerated tendon reflexes, ankle clonus, and a bilateral plantar extensor reflex. This condition subsided

within 36 hours. He continued on the same dose of iproniazid for a further five months, during which time he showed signs of increasing restlessness, euphoria, insomnia, and other mild toxic effects. He died in coma after an acute illness characterized by fever, coarse tremor, hallucinations, and "auditory delusions." At necropsy the brain showed that death was due to haemorrhagic encephalitis; since no other cause was apparent this was believed to be due to the toxic effect of iproniazid.

The toxic manifestations of the central nervous system caused by pethidine and iproniazid are similar: cerebral excitation, confusion, restlessness, and muscle twitchings are common to both. It is difficult to decide whether in our own and Mitchell's case cerebral symptoms were caused by the simple additive effect of the two drugs or by a more complex inhibition of the enzyme-detoxicating system in the liver. The problem, however, is of theoretical interest. It is of practical importance that the two drugs become incompatible once a certain level of iproniazid is reached in the tissues. This may take up to four weeks.

The response to chlorpromazine was remarkable and perhaps a life-saving measure in our patient. Barbiturates commonly invoked in the treatment of cerebral excitation did not help, and in larger doses could have done actual harm if, as we have suggested, the liver detoxicating system was affected by iproniazid.

Although the pharmacological action on the heart is not yet clearly established, the improvement in this case and in others still under observation suggests that iproniazid is a promising drug in the treatment of angina. Patients with decubital angina, however, need heavy sedation with morphine analogues and barbiturates; potentiation with iproniazid may give rise to toxic cerebral reactions as in our patient. It is because of such therapeutic implications that this case is reported.

Summary

A case of decubital angina treated with iproniazid is reported. Although the frequency of the attacks diminished, occasional pethidine injections were still needed for the relief of pain. During the fifth week of iproniazid treatment these injections were followed by signs of severe cerebral irritation and excitement which responded dramatically to chlorpromazine. Either the simple additive effect of the two drugs or more complex interference with the normal detoxication of pethidine in the liver by iproniazid is believed to have caused toxic cerebral damage. It is suggested that pethidine should be used with caution in patients on iproniazid treatment.

ADDENDUM.—Since this paper was submitted a different complication of iproniazid treatment has been encountered in a 63-year-old man suffering from incapacitating angina of effort. On a dose of 50 mg. twice daily, much improvement resulted. One month later, while still on the same dose, he complained of difficulty of micturition and giddiness, and his blood pressure had fallen from 140/80 to 110/75. Iproniazid was discontinued, and then resumed after one week. A fortnight later he developed a small cerebral thrombosis, from which he fortunately recovered. Hypotension caused by iproniazid may have precipitated this complication.

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TREATMENT OF ULCERATIVE COLITIS WITH LOCAL HYDROCORTISONE HEMISUCCINATE SODIUM

A REPORT ON A CONTROLLED THERAPEUTIC TRIAL

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With an Appendix by M. H. HAMBLING, M.B., B.S.

Two previous studies have dealt with the use of hydrocortisone applied topically to the colon in ulcerative colitis by means of a nightly rectal drip (Truelove, 1956, 1957). In the first study, 21 mild or moderate attacks of the disease were treated with hydrocortisone in the form of the free alcohol, and there were 14 rapid remissions, these remissions usually occurring in the first few days of treatment. However, although the sigmoidoscopic findings showed improvement in parallel with the clinical response, the histological picture as judged by biopsy specimens was little altered. As hydrocortisone itself is poorly soluble in water, the actual solution used for the rectal drip was prepared by diluting hydrocortisone dissolved in 50% ethyl alcohol with 10 times its volume of saline. There was the possibility that the weak alcoholic solution used as the vehicle for the hydrocortisone prevented the mucosa from healing.

In the second study, a compound freely soluble in water, hydrocortisone hemisuccinate sodium, was used. The clinical response was similar to that obtained with hydrocortisone itself in that there were 11 rapid remissions out of 18 courses of treatment. However, the histological picture of the colonic mucosa showed a favourable response in those subjects enjoying clinical remission, and it was therefore decided that the hemisuccinate (or some other water-soluble compound) was the corticoid of choice for this form of treatment.

The view that hydrocortisone applied topically is a useful form of treatment in this disease could be only presumptive on the results so far mentioned. In other words, this view rested solely on a personal clinical judgment that no considerable proportion of patients with an attack of ulcerative colitis would go swiftly into remission unless the treatment was having some strongly positive effect. Any student of ulcerative colitis must view with scepticism the use of a treatment based upon personal impressions, for the history of the disease includes a large variety of treatments which in their turn were introduced with enthusiasm on the strength of a few favourable responses and then slowly abandoned when they were found to be ineffective. The disease is one which manifests itself by exacerbations and remissions which are often unpredictable. Furthermore, a large body of opinion regards it as a psychosomatic disorder, so that a new form of treatment might possibly be beneficial for reasons unconnected with the pharmacological actions of the therapeutic agent. It is therefore essential that new forms of treatment should be put to formal tests so that patients are not exposed unnecessarily to useless methods of treatment.

Objects of the Present Study.—The main object of the present study was to compare the effect of hydro-

cortisone hemisuccinate sodium used topically with an inert preparation which resembled it superficially. The second object was to form an impression whether the combined use of hydrocortisone and antibiotics was better than hydrocortisone used alone. The third object was to determine whether patients who went into remission with local treatment would remain relatively free from relapse if they received maintenance treatment on two nights a week.

Method

The study comprised three parts, corresponding to the three objects of the trial.

Part I. Blind Controlled Trial of Local Treatment Lasting One Week

Patients with active symptoms of ulcerative colitis were allotted in a random order to treatment with either preparation A or preparation B, one of which was actual hydrocortisone hemisuccinate sodium while the other was an inert replica. These preparations were made and labelled by Glaxo Laboratories, and their identity was unknown to all the other persons concerned in the trial until after its conclusion. Treatment was prescribed in the following form:

A. J. Smith
U. C. No. 23

℞ Special rectal drip nightly for seven nights.

Patients were numbered consecutively as they entered the trial, and the hospital pharmacist entered their names on a prepared list that showed which preparation a patient with any particular serial number was to have. Treatment consisted in dissolving the contents of one ampoule of A or B in 120 ml. of normal saline and dripping the solution into the rectum at night. No other treatment was used.

The inert preparation was made by the manufacturers by freeze-drying concentrated dextran solution put up for intravenous use. The resulting powder closely resembled the preparation of hydrocortisone hemisuccinate sodium used in the trial. Each ampoule of inert preparation consisted of 20–30 mg. of freeze-dried dextran, which corresponded in volume to 100 mg. of hydrocortisone in the form of the hemisuccinate sodium ester. On general principles we should expect this small amount of intravenous dextran in 120 ml. of saline to be harmless to the colonic mucosa, and practical tests on patients with ulcerative colitis immediately after going into remission support this view.

Part II. Open Use of Hydrocortisone and Antibiotics for Two Weeks

At the end of the first week all patients were given nightly rectal drips of known hydrocortisone and antibiotics. Penicillin, 1 mega unit, and streptomycin, 1 g., were added to the hydrocortisone solution, which contained the hemisuccinate in an amount equivalent to 100 mg. of hydrocortisone itself. In 10 instances neomycin in a dose of 250 mg. was used in place of penicillin and streptomycin.

Part III. Blind Controlled Trial of Maintenance Treatment Employing Rectal Drips Twice a Week Over the Course of Six Months

Patients who were in clinical remission at the end of Part II were admitted to the maintenance part of the trial. The practical arrangements were analogous to those used in Part I in that Glaxo Laboratories supplied preparations labelled X and Y, one of which was actual hydrocortisone and the other was inert. In the earlier stages of this part of the trial neomycin or an inert replica, labelled as antibiotic X or antibiotic Y, was used in combination with hydrocortisone or its "dummy," but this was later given up for reasons set out below.

Selection and Assessment of Cases

Only patients with active symptoms from ulcerative colitis were admitted to the trial. As in the previous studies, severe cases with much constitutional disturbance were excluded. Many of the patients were ambulant and were treated as out-patients, although some were in hospital.

Some patients who went into remission but who relapsed during or after maintenance therapy were readmitted to the trial, once again being allotted to treatment A or B at random.

The clinical condition immediately before treatment was recorded. All patients were examined by sigmoidoscopy on the day when treatment began, and the findings were recorded. During this examination a mucosal biopsy was performed by means of an improved version of an instrument devised for serial biopsy (Truelove *et al.*, 1955) and a swab was taken from the lower colonic mucosa for bacteriological study.

At the end of Part I and of Part II of the trial, exactly similar observations were made. They were also made during Part III (trial of maintenance therapy), although they might be limited to the final attendance six months after the conclusion of Part II.

Barium-enema studies were not made as a routine. In every patient at least one barium-enema examination had previously shown evidence of ulcerative colitis. This examination not infrequently causes an exacerbation of symptoms. The patients are usually young and suffer from a disease from which they are likely to have future attacks in the course of which further *x*-ray studies may be essential. Many of them are women in the reproductive years of life, and unnecessary gonadal exposure to *x*-radiation is to be avoided. For all these reasons, the barium enema should be used sparingly in ulcerative colitis.

Forty courses of treatment were given, it being arranged beforehand that 20 would be with preparation A and 20 with preparation B during Part I of the trial. In the interests of brevity, individual case histories are not recorded.

Part I. Controlled Trial of Local Hydrocortisone Treatment

Clinical Response.—The clinical response to the two preparations is given in Table I. It can be seen that there is a striking difference between the clinical response shown with inert treatment and that with actual hydrocortisone, only 1 in 20 treatments with a "dummy" resulting in clinical remission, compared with just over one-half with hydrocortisone. In statistical terms, the difference is highly significant, as it would occur by chance less than 1 in 100 times.

TABLE I.—*Clinical Results of One Week's Treatment With Hydrocortisone or an Inert Preparation*

Treatment Group	No. of Patients	No. Symptom-free	Test of Significance
A (Inert therapy)	20	1	$\chi^2_c = 9{\cdot}6$, $n = 1$, $P = 0{\cdot}01$
B (Hydrocortisone hemisuccinate) ..	20	11	

χ^2 calculated with Yates's correction for continuity in view of the small numbers involved.

Sigmoidoscopic Responses.—The sigmoidoscopic findings resembled the clinical responses in showing a marked preponderance of favourable changes among the group receiving actual hydrocortisone. Once again the results are statistically highly significant (Table II). It is worth mentioning that there was almost perfect agreement between a good clinical response and a clear-cut sigmoidoscopic improvement. All the patients going into clinical remission showed improved sigmoidoscopic appearances. The only discrepancy was that one patient in each treatment group

TABLE II.—*Sigmoidoscopic Response to One Week's Treatment With Hydrocortisone or an Inert Preparation*

Treatment Group	No. of Patients	No. Showing Definite Improvement	Test of Significance
A (Inert)	20	2	$\chi^2_c = 8{\cdot}9$, $n = 1$, $P < 0{\cdot}01$
B (Hydrocortisone)	20	12	

showed improved sigmoidoscopic appearances even though they were not in clinical remission. Both later became symptom-free.

Histological Response.—Before treatment all the biopsy specimens taken at 15–20 cm. from the anal margin showed inflammatory changes of the type associated with ulcerative colitis. They have been classified as showing severe, moderate, or mild inflammation, according to the criteria employed by a pathologist colleague in a previous study (Truelove and Richards, 1956). Table III shows the histological picture as judged from biopsy specimens in each treatment group before and after the one week's controlled trial. Before treatment the two groups of patients were closely similar in respect of the histological changes. After treatment the histological picture in group A (inert therapy) was for all practical purposes identical with that before treatment. In group B (real therapy) there was a definite swing towards histological mildness. In statistical terms this group was significantly better histologically after treatment than it was before ($P<0.02$) and was also significantly better than group A after treatment ($P<0.05$). We may therefore justifiably conclude that topical hydrocortisone hemisuccinate exerts a favourable influence on the actual pathological picture of the colonic mucosa in ulcerative colitis (Fig. 1).

TABLE III.—*Histological Responses to One Week's Treatment With Hydrocortisone or Inert Preparation*

Treatment Group	Degree of Inflammation	Before Treatment	After Treatment	Significance of Differences Before and After Treatment
A (Inert therapy) ..	Severe	8	7	No significant difference
	Moderate	10	11	
	Mild	2	2	
B (Hydrocortisone hemisuccinate)	Severe	8	4	$\chi^2=8\cdot6$ n=2 $P<0\cdot02$
	Moderate	11	7	
	Mild	1	9	
Significance of differences between A and B		No significant difference	$\chi^2=6\cdot2$ n=2 $P<0\cdot05$	

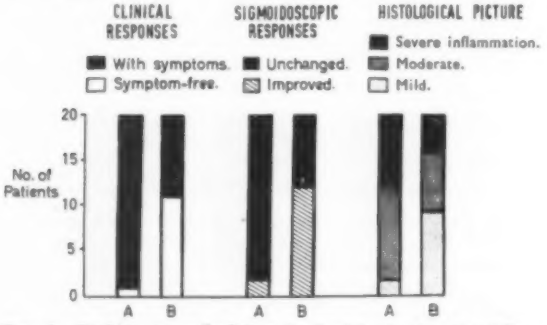

FIG. 1.—Position at end of Part I of trial, showing the differences in the clinical, sigmoidoscopic, and histological pictures after one week of topical treatment with either an inert preparation or real therapy. (A=Inert preparation. B=Hydrocortisone hemisuccinate sodium.)

Part II. Two Weeks' Treatment with Known Hydrocortisone and Antibiotics

Clinical Response.—At the end of another two weeks, when all patients had been treated with known hydrocortisone hemisuccinate and antibiotics used locally, the two treatment groups were closely similar in respect of their clinical state. In treatment group A, which began with only one patient in clinical remission, 12 patients went into remission during this period, making a total of 13 for the group. In treatment group B, which began this part of the trial with 11 patients in remission, another 5 became symptom-free, making a total of 16. The final difference between the two treatment groups is small, and would be expected to occur frequently by chance alone (Table IV).

TABLE IV.—*Clinical State at End of Part II of Trial, When All Patients Had Completed Two Weeks' Treatment With Known Hydrocortisone and Antibiotics*

Treatment Group	No. of Patients	No. Symptom-free	Test of Significance
A	20	13	$\chi^2=1\cdot1$ n=1 $P>0\cdot05$
B	20	16	

Sigmoidoscopic Response.—Once again the sigmoidoscopic appearances moved in parallel with the clinical response. All of the 29 patients who were free of symptoms at the end of the third week showed sigmoidoscopic appearances which were decisively better than when they began treatment. Some residual inflammation (as judged by gross appearances) was present in a number of these 29 patients, but in 18 the appearances were judged to be "normal" or "near-normal," the latter term implying that the only abnormality was a fine pin-point granularity not accompanied by hyperaemia or by increased mucosal fragility. Three of the 11 patients still having bowel symptoms at the end of three weeks' treatment showed sigmoidoscopic improvement, and in all three there had been lessening of the bowel symptoms, although they were not yet symptom-free. Table V shows that the two treatment groups A and B were closely similar at the end of the second part of the trial.

TABLE V.—*Sigmoidoscopic Appearances at End of Three Weeks' Treatment, the Last Two Weeks Having Been With Known Hydrocortisone and Antibiotics*

Treatment Group	No. of Patients	No. with Normal or Improved Sigmoidoscopic Appearances	Test of Significance
A	20	15	$\chi^2=0\cdot5$ n=1 $P>0\cdot05$
B	20	17	

Histological Response.—The histological responses likewise showed improvement in both treatment groups after known therapy, and there was little difference between them at the end of this part of the trial. The small advantage maintained by group B is not statistically significant (Table VI, Fig. 2).

TABLE VI.—*Histological Picture at End of Part II of the Trial*

Treatment Group	Degree of Inflammation	No. of Patients	Test of Significance
A	Severe	3	$\chi^2=1\cdot2$ n=2 $P>0\cdot05$
	Moderate	6	
	Mild .. Near-normal	11	
B	Severe	1	
	Moderate	6	
	Mild .. Near-normal	13	

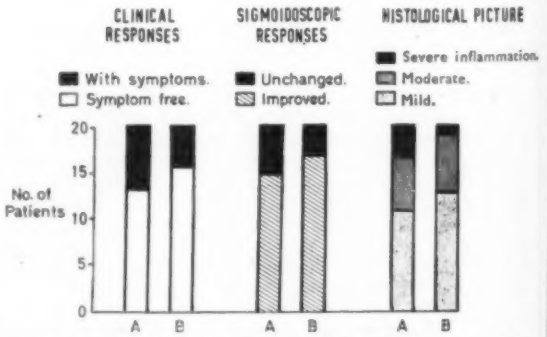

FIG. 2.—Position at end of Part II of trial, showing the similar clinical, sigmoidoscopic, and histological pictures after both treatment groups had received topical treatment with known hydrocortisone hemisuccinate sodium.

Action of Antibiotics Added to the Rectal Drip

The effect of antibiotics is not straightforward. The first thing to note is that in a few patients their use was attended by a sharp exacerbation of symptoms. In two of these cases it was known that the patients had previously had sensitivity reactions to penicillin given by injection, so that no great surprise was aroused when immediate symptomatic deterioration occurred. Both these patients had colonic biopsy specimens taken in the phase of flare-up, but the specimens showed only those changes which we associate with active ulcerative colitis; in other words, there was no specific recognizable change to be attributed to the penicillin. The antibiotics were stopped in these two patients, and they continued on the second part of the trial with hydrocortisone hemisuccinate alone; both went into clinical remission in this period. There were three other patients without known sensitivity reactions to any antibiotic who behaved in a similar manner. Two of these were among the 10 patients who were treated with neomycin in the drip instead of penicillin and streptomycin. One of them was already in remission when going into this second part of the trial, but she promptly relapsed on going on to known hydrocortisone and neomycin. On stopping the neomycin she rapidly became symptom-free, and remained so for some months. For this reason neomycin was discontinued for the remainder of the study.

On the other hand, there were some patients in whom it has been found that hydrocortisone alone did not have any appreciable effect during the first week of therapy but who improved rapidly when antibiotics were added to their treatment. (That such patients were on actual hydrocortisone during the first week has, of course, been known only since the study ended.) In parenthesis, it may also be added that similar favourable responses have been seen in a few instances among patients outside the present study who were being treated routinely with the rectal drip of hydrocortisone.

Consequently, there appear to be two conflicting factors at work. On the one hand, the inflamed colonic mucosa may sometimes react badly to the topical application of antibiotics in high concentration. On the other hand, some patients who are not responding to local hydrocortisone alone appear to do so promptly when antibiotics are added to the rectal drip. The net effect of these two opposing influences seems to be a small gain in the number of remissions achieved, if one can go on a comparison of the results obtained in the present study with those of the two previous studies of local hydrocortisone in ulcerative colitis (Table VII). The differences are not statistically significant, and

TABLE VII.—*Comparison of Results Obtained When Antibiotics are Added to the Rectal Drip of Hydrocortisone with Those Obtained with Hydrocortisone Alone*

	No. of Patients	Remissions		Test of Significance
		No.	%	
(I) Hydrocortisone (free alcohol) for 2–3 weeks (Truelove, 1956)	12	14	66·6	$\chi^2=0·8$ n=2 P>0·05
(II) Hydrocortisone hemisuccinate sodium for 2 weeks (Truelove, 1957)	18	11	61·1	
(III) Hydrocortisone hemisuccinate sodium plus antibiotics (present study)	40	29	72·5	

inspection of the figures is sufficient to discount any idea that the addition of antibiotics makes any major difference to the success of this form of treatment. Nevertheless, one can tentatively suggest the following working rules: (1) Antibiotics should not be used as a routine addition to a rectal drip of hydrocortisone hemisuccinate. (2) If no response is obtained with hydrocortisone alone in one week, it is worth trying the effect of adding antibiotics, and a mixture of penicillin and streptomycin seems preferable to neomycin. If the addition of antibiotics causes symptomatic exacerbation they should be stopped immediately. If the response is good, antibiotics can be continued for a week or 10 days, being then discontinued even if treatment with local hydrocortisone is to be maintained.

Of course, this opinion refers only to the use of high concentrations of antibiotics. It is possible that the use of lower concentrations might not cause exacerbations, but further work will be necessary to decide this.

Bacteriological Findings

Colonic swabs taken serially from the patients were examined bacteriologically by Dr. M. H. Hambling, who has summarized his findings in an Appendix to this article. The main object of this part of the study was to see whether the use of antibiotics frequently gave rise to colonic organisms insensitive to the antibiotics used, and, if so, whether this circumstance influenced the response to treatment. In brief, it can be said that resistant organisms sometimes appeared in the bowel, but their presence seemed to have no influence on the clinical response to local hydrocortisone.

Part III. Controlled Trial of Week-end Maintenance Therapy with Local Hydrocortisone for a Period of Six Months

Twenty-six of the patients who were symptom-free at the end of Part II of the trial were put on to maintenance treatment consisting of a rectal drip on two consecutive nights each week (week-end maintenance therapy). Of these, 13 received treatment with hydrocortisone hemisuccinate sodium (preparation Y) and 13 with the inert preparation (preparation X).

These two treatment groups did not differ in their liability to clinical relapse during the six months covered by this part of the trial. In each group of 13 patients there were five who suffered from clinical relapse accompanied by sigmoidoscopic and histological deterioration (Fig. 3). It has therefore been shown that week-end maintenance therapy with local hydrocortisone does not protect against relapse occurring.

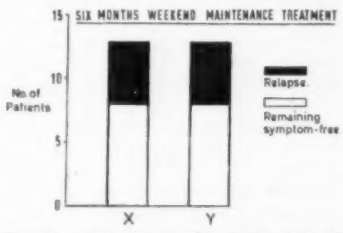

FIG. 3.—Position at end of Part III of trial, showing the similar state of patients given week-end maintenance therapy with either an inert preparation or real therapy. (X=Inert preparation. Y=Hydrocortisone hemisuccinate solution.)

However, it must be mentioned that among the 10 patients who relapsed during the maintenance part of the trial 9 rapidly became symptom-free with nightly rectal drips of hydrocortisone; the tenth did not respond to topical hydrocortisone alone, but did so promptly when oral prednisolone, 5 mg. four times a day, was given in addition.

Discussion

The present study has shown beyond all reasonable doubt that hydrocortisone hemisuccinate sodium administered in a rectal drip produces rapid clinical remissions in a considerable proportion of patients with mild to moderate attacks of ulcerative colitis. These clinical remissions are accompanied by improvement in the sigmoidoscopic appearances and by lessening of the inflammatory changes seen in colonic biopsy specimens. The experimental design of the trial permits the conclusion that the beneficial effect is a pharmacological one, because a control group receiving a placebo given under identical conditions showed a negligible number of favourable responses.

It is probable that the hydrocortisone hemisuccinate sodium acts chiefly by some direct effect upon the actual mucosa of the colon. In the first place, the beneficial effect commonly appears to be much more rapid than that observed with cortisone and its analogues used systemically. Secondly, some patients outside the present study have been maintained on nightly rectal drips of hydrocortisone hemisuccinate sodium for periods of several months without any clinical evidence of cortisonism. Thirdly, the preliminary

results of my colleague Dr. I. E. Bush suggest that only a comparatively small fraction of the hydrocortisone hemisuccinate sodium reaches the systemic circulation. Finally, and perhaps most convincingly, favourable clinical, sigmoidoscopic, and histological responses have been observed in patients with ulcerative colitis limited to the rectum and recto-sigmoid region by the use, once or twice a day, of suppositories containing only 10 mg. of hydrocortisone as the hemisuccinate. As some of these patients had previously suffered from attacks of classical ulcerative colitis involving a substantial part or the whole of the colon, there is no need to consider the possibility that they were not true examples of ulcerative colitis.

The therapeutic action would appear to resemble what happens in those skin diseases, such as atopic dermatitis, which respond favourably to topical application of hydrocortisone in a lotion or ointment. Absorption through the skin is very small, being of the order of 2%, so that the systemic effect is negligible, but the favourable results can be impressive, and have been shown by properly controlled studies (Sulzberger and Witten, 1954) to be directly due to the hydrocortisone. An analogous improvement of the buccal mucosa has been observed in patients with severe recurrent aphthous stomatitis who were receiving amounts of hydrocortisone hemisuccinate sodium too small to have any appreciable systemic effects (Truelove and Morris-Owen, 1958).

The addition of antibiotics to the rectal drip has turned out on balance to be beneficial in only a small proportion of patients. Although the weight of evidence is heavily against ulcerative colitis being a bacterial disease, there is little doubt that secondary bacterial infection is responsible for many of its most unpleasant complications. It seemed possible that the presence of bacterial infection might be the reason for some patients failing to respond to local hydrocortisone treatment. As it has been shown by elegant experiments that an infected atopic dermatitis may respond neither to local hydrocortisone alone nor to local antibiotics alone but will respond when the two are used together (Robinson *et al.*, 1956), it was hoped that an analogous response might be obtained in ulcerative colitis. In the event, the gain from adding antibiotics to the rectal drip of hydrocortisone has appeared to be small, and sharp exacerbations have occurred in a few patients from the direct application of antibiotics to the inflamed colon.

Although some patients enjoy a prolonged remission after a short course of local hydrocortisone, about two-fifths of the patients have a recurrence of symptoms in the course of the next six months and require further treatment. This fact illustrates the major problem in the management of ulcerative colitis to-day. By one method or another most attacks of ulcerative colitis can be brought under control by medical methods and the patient rendered symptom-free. However, once a patient has suffered from an attack of ulcerative colitis he is extremely liable to have subsequent attacks, and we know of no method to prevent them. The part of the present study which concerned maintenance therapy was designed to see whether, once a patient had been brought into clinical remission with local hydrocortisone, he could be held in remission by means of local treatment given on two consecutive nights a week only (week-end maintenance treatment). The answer is a decisive "No." A more fruitful approach to the problem may be to give a much more prolonged initial course of local treatment in those patients who respond well to it, in the hope that the colon will become more permanently improved by this means.

Outside the present study, a number of patients have been on prolonged treatment with nightly rectal drips of hydrocortisone, and the results so far appear to be very favourable, not only as regards the immediate benefits but also with respect to the production of a long-lasting remission. However, more patients need to be treated and to be observed for longer periods before this important question can be answered with any degree of assurance. Alternatively, the liability to recurrent attacks can be accepted and each one can be treated as it arises. When a patient has once responded well to local hydrocortisone it is likely that he will do so in subsequent attacks, and a number of patients have now been kept free of any major disability by intermittent courses of treatment given whenever clinical relapse occurred.

Although the present study has shown topical hydrocortisone hemisuccinate sodium to have a genuinely favourable effect in ulcerative colitis, it remains to be seen whether this form of treatment is superior to others which have been shown to be of value in cutting short attacks of the disease, such as corticoids used systemically. My impression is that local hydrocortisone hemisuccinate sodium scores over corticoids used systemically by the rapidity with which favourable responses are obtained and by the absence of any evidence of systemic side-effects of therapy. At present, my experience of this form of treatment extends to its use in about 100 patients, a number of whom have had more than one course of treatment, while some others have been on treatment for periods of several months consecutively. There have been no side-effects discernible clinically and no complications. In my own experience, therefore, the method has proved entirely safe.

Although this and the two previously published studies have been concerned with the less severe attacks of ulcerative colitis, it should not be thought that local hydrocortisone hemisuccinate sodium is valueless in the severe attacks. A number have been treated, and the results have been most encouraging. However, the local treatment of severe attacks raises certain problems, one of which concerns methods of ensuring that the therapeutic agent is retained in the colon. Propantheline bromide, given intravenously, is one agent which has been used to assist in retention. Heavy sedation of the patient and elevation of the foot of the bed also help. But these are issues which lie outside the province of the present study, which is concerned mainly with a formal demonstration that topical hydrocortisone hemisuccinate sodium is an effective form of treatment for a large proportion of patients with mild or moderate attacks of ulcerative colitis.

Summary

A formal therapeutic trial has been conducted to show whether topical hydrocortisone hemisuccinate sodium has a genuinely beneficial action in ulcerative colitis.

In the first part of the trial a controlled comparison was made of hydrocortisone and an inert preparation which resembled it in appearance. At the end of one week of treatment the patients receiving hydrocortisone therapy showed a striking advantage over those on the inert preparation, not only in respect of the clinical state but also as regards the sigmoidoscopic appearances and the histological appearances of colonic biopsy specimens.

All patients were then given open therapy with topical hydrocortisone and antibiotics used in conjunction for two weeks. About three-quarters of the patients were in clinical remission at the end of this period. By comparison with other studies in which antibiotics were not used, the addition of antibiotics seems to confer a small gain in the number of successes with topical hydrocortisone therapy, although at the price of a few patients developing exacerbation of symptoms.

Twenty-six of the patients who were in clinical remission after open therapy were entered for a trial week-end maintenance therapy lasting six months. Thirteen of the patients received hydrocortisone and the other 13 an inert preparation. The clinical course of the two groups was identical, each having five patients who relapsed during the six-months period. Week-end main-

tenance therapy with local hydrocortisone is therefore ineffective in reducing the chance of relapse.

The implications of these various findings are briefly discussed.

I am indebted to Glaxo Laboratories, who not only made a gift of the hydrocortisone hemisuccinate sodium and the inert preparation, but also packed and labelled them ready for use in this trial. I am also indebted to the Medical Research Council for a grant for technical assistance. I wish to thank the following colleagues: Dr. M. H. Hambling for conducting the bacteriological studies; Dr. R. L. Vollum and Dr. W. H. H. Jebb for advice on antibiotics and bacteriology; Miss H. Enser, who assisted me in the sigmoidoscopic examinations and prepared the histological specimens; Miss M. G. Craig and Miss S. V. James, who issued the various therapeutic agents according to the prepared plan; and Miss M. C. McLarty, who made the Charts.

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APPENDIX: BACTERIOLOGY OF THE COLONIC SWABS

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Methods

At each examination the pelvic colon was swabbed through the sigmoidoscope. Bacteriological examination of the swab was made: (1) to exclude intestinal pathogens of the Salmonella and Shigella groups; and (2) to determine the antibiotic sensitivities of the predominant organisms in order to detect any marked increase of resistant strains following rectal antibiotic therapy.

Each swab was shaken with 5 ml. of digest heart broth, and a loopful of the broth was inoculated to each of the following media:—*Solid media:* Two blood-agar plates (one for anaerobic incubation), a deoxycholate citrate agar plate and a MacConkey agar plate. *Fluid media:* A Robertson's cooked-meat medium, and a Robertson's cooked-meat medium to which 10% NaCl had been added.

Finally 5 ml. of selenite F (Leifson, 1936) was added to the remainder of the broth and all cultures were incubated at 37° C. overnight.

The following day the plates were examined. The Robertson's cooked-meat medium was plated to two blood-agar plates (one for anaerobic incubation), one deoxycholate citrate agar plate, and one MacConkey agar plate; the Robertson's cooked-meat medium containing salt was subcultured to a plate of nutrient agar containing 7% salt and to a blood-agar plate (for aerobic incubation). The selenite F broth was plated to a deoxycholate citrate agar plate. All the plates were then incubated overnight at 37° C.

No special media were used in an attempt to isolate yeasts, lactobacilli, or anaerobic Gram-negative rods.

The organisms most frequently isolated were lactose-fermenting Gram-negative rods (L.F.s), *Streptococcus faecalis*, *Clostridium welchii*, *Staphylococcus aureus*, micrococci, Proteus, and paracolon organisms; and of these, L.F.s and *str. faecalis* were the most common.

The Gram-negative rods were examined for sensitivity to streptomycin and neomycin, while the Gram-positive organisms were tested against penicillin and neomycin.

Findings

1. No member of the Salmonella or Shigella groups was isolated from any of the 137 specimens examined.

2. Lactose-fermenting Gram-negative rods isolated from the 30 patients treated with rectal penicillin and streptomycin tended to show an increased resistance to streptomycin. Before treatment, 34 strains of L.F.s were isolated of which 4 were sensitive to 25 units of streptomycin per ml., and 30 sensitive to 12 or less units of streptomycin per ml.; whereas after treatment 24 strains were isolated, of which 7 were resistant to 100 units of streptomycin per ml., 1 was sensitive to 50 units of streptomycin per ml., 3 were sensitive to 25 units of streptomycin per ml., and the remaining 13 strains were sensitive to 12 or less units of streptomycin per ml. Strains of *Str. faecalis* isolated before and after treatment showed no increased resistance to penicillin.

3. Strains of *Staph. aureus* were isolated from eight patients, but in no case was a penicillin-sensitive strain replaced by a penicillin-resistant strain, and in only one patient (an in-patient) was *Staph. aureus* isolated from every specimen.

Colonic swabs from the smaller series of patients who were given neomycin rectally were subjected to the same culture routine as above, but in no case were neomycin-resistant organisms isolated.

Summary

Bacteriological examination of 137 colonic swabs failed to isolate any member of the salmonella or shigella groups.

Following rectal administration of streptomycin, penicillin, and neomycin it appeared that a few strains of lactose-fermenting Gram-negative rods showed increased resistance to streptomycin, but no Gram-positive organisms showed increased resistance to penicillin or neomycin.

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TREATMENT OF ULCERATIVE COLITIS WITH TOPICAL HYDROCORTISONE HEMISUCCINATE SODIUM

A CONTROLLED TRIAL EMPLOYING RESTRICTED SEQUENTIAL ANALYSIS

BY

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The many reports indicating that systemic corticoid therapy was of value in the treatment of ulcerative colitis, and the fact that topical hydrocortisone had been used successfully in various eye, joint, and skin diseases, made it possible that mild cases of colitis would respond to this method of treatment.

Favourable reports of the use of topical hydrocortisone in colitis have already appeared (Truelove, 1956, 1957). These results were considered by him to be encouraging enough to merit a controlled trial of this form of treatment of colitis.

A controlled trial has therefore been undertaken where the relative merits of solutions of hydrocortisone hemisuccinate sodium and an inert preparation administered rectally to patients with haemorrhagic proctocolitis and ulcerative colitis have been assessed in a blind controlled trial. In order to obtain a significant answer as rapidly as possible a method of restricted sequential analysis devised by Dr. Peter Armitage has been used in the planning and control of the trial. A significant advantage in favour of the potent hydrocortisone has been demonstrated by 19 treatments in 16 patients with colitis where symptomatic remissions and sigmoidoscopic improvement occurred significantly more commonly in those receiving potent therapy. The

responses of patients receiving potent and dummy treatments are first contrasted and later the method of sequential analysis of the results obtained is detailed.

Method of Administration

Glaxo Laboratories were kind enough to provide potent and inert agents for the trial, labelled Y and X respectively. Treatment was administered to patients as follows: 100 mg. of hydrocortisone hemisuccinate sodium or the dummy preparation was dissolved in 100 ml. of normal saline. It is important that the solution be freshly prepared before use, as slow hydrolysis occurs and causes some of the hydrocortisone to precipitate out of the solution on standing. The patient lies on his left side, and the solution is then administered through an intravenous drip set attached to a rectal catheter at a fairly rapid drip rate of one to two drops per second over a period of 15 to 30 minutes. The rectal infusion is retained overnight and is repeated on 15 successive evenings. Usually the technique was rapidly mastered by the patients receiving it, and after two to three nights of treatment in hospital they returned home and continued nightly infusions there.

In more severely affected patients in whom nocturnal diarrhoea might prevent the retention of the infusion an intravenous injection of propantheline, 15–30 mg. half an hour before the infusion, was given to aid retention overnight.

Patients Treated

Sixteen patients with haemorrhagic proctocolitis or colitis were treated on 10 occasions with potent therapy and on nine with an inert preparation, three patients being treated twice. Treatments were allocated in random fashion to both groups, as is described later. All patients gave typical histories of recurrent diarrhoea and blood-stained stools, and showed mucosal changes on sigmoidoscopy which were consistent with the diagnosis. Barium-enema examinations were undertaken in each patient to assess the extent of colonic involvement. Precise clinical information on the age and sex, duration of history, and extent and severity of the disease is given in Tables I and II, and is summarized

TABLE I.—*Patients Receiving Hydrocortisone*

Treatment No.	Sex and Age	Duration of History	Extent of Disease*	Pre- and Post-treatment Assessments						Comment	Progress
				Hb	E.S.R.	Stools Daily	Blood	Mucus	Sig.†		
1	M 28	2 years	R.S.	—	—	6	++	++	3	Remission	Maintained for 6 months
				—	—	1	—	—	1		
2	M 59	2 ,,	R.S.D.	69	30	7	+++	+	4 (u)	Remission in severe acute colitis with associated ankylosing spondylitis. Mucosa restored to normal	Remission maintained clinically and sigmoidoscopically for 6 months
				98	20	1	—	—	1		
4	M 37	6 ,,	R.S.	90	—	6	++	+	2	Symptomatic remission without sigmoidoscopic improvement	Sigmoidoscopic appearances improved after 2 months. Clinical and sigmoidoscopic relapse at 6 months. Second course induced remission
				95	—	2	—	—	3		
6	F 28	4 ,,	R.S.	90	12	3	+	+	3	Symptomatic remission. Mucosal improvement	Remission maintained for 5 months
				95	8	2	—	—	2		
9	F 48	1 year	R.S.D.	79	15	8	+++	+	3	Failure—slight improvement	Relapse in 1 month. Received second course of dummy therapy
				70		5	+	+	2		
11	F 49	1 ,,	R.S.D.	85	6	2	+++	+	3	Clinical remission. Mucosal improvement. Associated duodenal ulcer	Remission maintained for 3 months
				90	6	1	—	—	1		
13	F 20	3 years	R.	93	15	5	++	+	3	Clinical remission. Mucosal improvement	Mild relapse after 3 months
				95	5	1	—	—	2		
15	F 53	25 ,,	R.S.	73	15	6	++	++	3	,, ,, ,,	Remission maintained for 6 months, when mucosa found to be normal
				85	5	1	—	—	2		
16	M 74	½ year	R.	74	—	5	+++	+	4 (u)	Clinical remission. Considerable mucosal improvement	Remission maintained for 6 months. Mucosa still remained improved (2)
				90	—	2	—	—	2		
18	F 41	7 years	R.S.	69	18	5	+	++	3	Clinical remission. Restoration of mucosal normality	Remission still maintained at 2 months
				87	12	1	—	—	1		

* *Extent of Radiological Changes:* R = Rectum only; no *x*-ray changes. R.S. = Rectum and sigmoid colon. R.S.D. = Rectum, sigmoid, and descending colon.
† *Sigmoidoscopic findings:* 1 = Normal mucosa. 2 = Mild granularity with minimal contact bleeding. 3 = Marked granularity and contact bleeding. 4 = Spontaneous rectal haemorrhage, ulceration (u).

TABLE II.—*Control Cases*

Treatment No.	Sex and Age	Duration of History	Extent of Disease*	Pre- and Post-treatment Assessments						Comment	Progress
				Hb	B.S.R.	Stools Daily	Blood	Mucus	Sig.†		
3	M 65	20 years	R.S.D.	80	10	3	++	+	3	Slight improvement	Relapse in 2 months
				85	10	2	+	—	3		
5	F 25	1 year	R.S.	65	15	10	++	++	3	Improved. Received second course dummy preparation	Relapse in 1 month
				76	9	5	+	+	2		
7	M 34	2 years	R.S.	88	12	3	++	+	3	Worse after treatment	Improved spontaneously in 3 months
				90	15	7	++	+	3		
8	F 48	25 ,,	R.	90	5	2	++	+	3	Slight improvement	Relapse in 2 months
				87	5	2	+	—	2		
10	F 25	1 year	R.S.	75	11	6	++	++	3	Failure	Relapse in 1 month. Given potent therapy
				80	10	6	++	++	3		
12	F 35	1 ,,	R.S.D.	82	25	6	++	+	4 (u)	,,	Some improvement followed systemic treatment with corticotrophin but condition still unsatisfactory and surgery undertaken
				74	30	6	++	++	4 (u)		
14	F 53	25 years	R.S.	85	—	6	+++	+	3	,,	Relapse in 2 months. Given potent therapy
				85	—	3	+	—	2		
17	F 66	6 mths	R.S.	89	20	7	++	+	3	Clinical remission. Mucosa unchanged	Remission maintained for 2 months
				90	20	2	—	—	3		
19	F 48	1 year	R.S.D.	75	35	10	++	+	3	Failure	Treatment abandoned after 5 infusions. Some improvement followed corticotrophin and "salazopyrin." Condition still unsatisfactory; surgery may be necessary
				70	30	15	++	+++	3		

* † See footnotes to Table I.

in Table III, where those receiving potent and inert therapy are contrasted. It will be seen that the two groups of

TABLE III.—*Comparison of Effects of Topical Hydrocortisone with Dummy Preparation in Haemorrhagic Proctocolitis and in Ulcerative Colitis. Potent and Dummy Treatments Allocated in Random Manner to 16 Patients*

		Potent Therapy	Control Cases
No. of treatments		10	9
Ages		(4 males, 6 females) 20–74 years	(2 males, 7 females) 25–66 years
Extent of disease	Rectum	2	1
	Rectum and sigmoid colon	5	5
	Rectum, sigmoid, and descending colon	3	3
Duration of history	<1 year	1	1
	1–2 years	4	5
	3–4 ,,	2	0
	5 years+	3	3
Ulcerative lesions		2	1

patients treated are surprisingly similar in age, sex distribution, extent of disease, and duration of history. Two patients with more severe ulcerative lesions were treated with potent therapy and one with inert drug.

Method of Investigation

In all cases a clinical assessment of the patient's condition was made personally by an inquiry into the severity of diarrhoea and the blood content of the stools, the observer being unaware of the treatment given. A haemoglobin and an erythrocyte sedimentation rate were determined before and after treatment. Sigmoidoscopic examinations were performed before treatment and within two or three weeks of completion of the course of infusions. These examinations were made by an independent observer (Professor J. C. Goligher), who was also unaware whether potent or dummy treatment was being given. As will be seen, the clinical response of the patients receiving hydrocortisone (Table I) was strikingly better than those receiving inert therapy (Table II). In most patients receiving hydrocortisone the stools rapidly became normal; usually within two to three days of starting treatment blood disappeared from the stools and an improvement in the patient's general condition was shown by increased well-being and a rise in haemoglobin level and reduction in the erythrocyte sedimentation rates. The sigmoidoscopic appearances often returned to normal, but were improved in most of the cases going into clinical remission. Table II shows that inert therapy was strikingly ineffective: diarrhoea, if anything, was worse after treatment; haemoglobin and E.S.R. levels were unchanged or rather worse; and sigmoidoscopic appearances showed no change or a deterioration.

The overall results obtained in 19 treatment periods are summarized in Table IV. Of 10 patients receiving potent therapy all but one went into clinical remission as compared with only one out of nine patients receiving inert treatment. Two, however, showed slight improvement after inert

TABLE IV.—*Topical Hydrocortisone in Ulcerative Colitis. Results of Treatment*

		Potent	Control
Clinical	Remission	9	1
	Improvement	—	3
	No change or worse	1	5
Mucosal appearances	Normal	3	—
	Improvement	6	3
	No change or worse	1	6
Remission maintained	1–2 months	2	2
	3–5 ,,	3	—
	6–9 ,,	4	—
Relapses		3	7

therapy. Mucosal appearances became normal in 3 and improved in 6 of the 10 patients receiving the potent agent, and contrasted markedly with those receiving the dummy treatment, where only three showed slight improvement. It has not been definitely established how long remission will be maintained after an initial course of treatment, but 4 of the 10 patients treated with hydrocortisone have remained in clinical remission for six to nine months. Three relapses have already occurred but have responded to further courses of treatment. The one patient showing remission on dummy therapy relapsed within a month of stopping treatment.

The response of three patients who were treated in the trial by both agents is of interest.

Case A: Courses 5 and 10.—A woman aged 25 gave a history of rectal bleeding, diarrhoea, and mucus discharge for one year, and sigmoidoscopy confirmed the presence of a haemorrhagic proctosigmoiditis. An initial course of dummy treatment effected a slight improvement with a reduction of the frequency of diarrhoea from ten to five stools daily and a lessening of rectal bleeding. Relapse occurred within one month and the patient re-entered the trial. She was unfortunate enough to be allocated a further course of dummy treatment, which had no effect upon her diarrhoea. She continued to pass six loose stools daily which contained more blood than before treatment was given. Mucosal appearances also worsened. Potent therapy was given outside the trial and induced a rapid clinical remission, with a reduction of stool frequency from six to two daily, a disappearance of blood from the stools, and an improvement in the mucosal appearance. A mild relapse has occurred in this patient after two months.

Case B: Courses 14 and 15.—A woman aged 53 gave a history of recurrent rectal bleeding, mucus discharge, and diarrhoea for 25 years. Sigmoidoscopy again confirmed the presence of a haemorrhagic proctosigmoiditis. An initial course of dummy treatment effected a slight improvement in the character of the stools and mucosal appearance, but relapse occurred within two months. A course of potent drug caused a striking clinical remission with a reduction of stool frequency from six to one daily and a disappearance of rectal bleeding. Mucosal appearances were improved.

Case C: Courses 9 and 19.—A woman aged 48 gave a history of ulcerative colitis for one year and severe mucosal inflammation, and ulceration was confirmed sigmoidoscopically. Treatment with the potent drug initially induced a slight improvement, with a reduction of bowel action from eight to five stools daily and a lessening of rectal bleeding. Mucosal inflammation was less marked after treatment. A severe relapse, however, occurred after one month, and treatment on a second occasion by dummy therapy considerably worsened the patient's diarrhoea and the appearances sigmoidoscopically. This patient showed some improvement with systemic corticotrophin, but required surgery to control her symptoms.

It will be seen that two of these patients serving as their own controls showed appreciable advantages in favour of potent therapy. The third patient did not seem particularly responsive to any form of corticoid treatment, but certainly fared better with potent than with dummy treatment. The successful outcome of potent therapy in the majority of patients treated is therefore clearly apparent. A method of sequential analysis used to demonstrate significant differences between the forms of treatment is now detailed.

Sequential Analysis

The statistical technique of restricted sequential analysis has been developed in particular relation to therapeutic trials by Dr. Peter Armitage, and formerly has been used to establish the relative merits of analgesics and cough-suppressive agents (Armitage, 1954, 1957; Newton and Tanner, 1956; Snell and Armitage, 1957). Treatments are allocated to pairs of patients in a random order, and the course of the trial is followed by accumulating the qualitative comparisons between treatments which are provided by each pair of patients. Results are recorded on a chart while the trial is in progress, the boundaries of which determine the minimum number of observations necessary to establish a significant advantage in favour of one treatment. Alternatively, other specified limits indicate that if no significant difference emerges when a certain number of pairs of patients have been treated the trial should be abandoned.

Sequential analysis is therefore the method most economical of patients and of time in the comparison of two treatments, and seemed admirably suited to compare the relative merits of hydrocortisone and a dummy prepara-

tion in the treatment of colitis. By this method the significant advantage of potent treatment has been established in the strikingly small number of 19 treatment periods. Dr. Peter Armitage was kind enough to devise a chart suitable for the trial and to suggest the method of random allocation of the treatments given. Without his generous help the trial could not have been undertaken in this particular form.

Method of Random Allocation

A master sheet was prepared and held by the pharmacist dispensing the two forms of treatment. Pairs of patients, one receiving potent and one receiving dummy preparations, were first paired by the system of random numbers shown below, which is seen to be different for each group of 10 patients studied. The order of treatments given to each pair was determined by the spin of a coin, the next patient entering the trial receiving the alternative treatment and completing each pair. In this way a doubly randomized method of selection was ensured. Pairs of randomized treatments were as follows :

Patient's No.:	1	2	3	4	5	6	7	8	9	10
	P	P	D	P	D	P	D	D	P	D
	11	12	13	14	15	16	17	18	19	20
	P	D	P	D	P	P	D	P	D	D

P = Potent. D = Dummy treatments.

Both patient and physician were unaware of the nature of the treatments given until the course had been completed. Patients told that the relative merits of two unproved therapeutic agents in colitis were being compared, and that they stood even chances of receiving either, agreed willingly to participate in the trial.

Method of Sequential Analysis

The outcome of treatment in the pairs of patients studied is one of the four types indicated in Table V. Potent or inert therapy might be equally successful or ineffective : these are termed "tied" pairs and show no particular advantage for one agent and are not recorded on the chart. Pairs of subjects, where potent or inert therapy is effective in one instance and fails in the other, are termed "untied" pairs, and are recorded on the control chart as a point in favour of one form of treatment. The comparative frequencies of symptomatic remission and mucosal improvement assessed sigmoidoscopically are summarized in Table V, and provided information for separate control charts.

TABLE V

	"Tied" Pairs		"Untied" Pairs	
Potent	+	−	+	−
Dummy	+	−	−	+
Symptomatic remission ..	2	1	6	—
Sigmoidoscopic improvement	—	2	7	—
Method of recording on chart	Not used in investigation		Plot as point in favour of potent drug	Plot as point in favour of dummy preparation

Similar success or failure occurred in five pairs of patients which were not used in the investigation. The number of "tied" pairs is the only factor which cannot be predicted in advance in this type of trial. The frequency of "tied" pairs in this trial is remarkably small, as it might have been expected that similar numbers of pairs of patients might be "tied" or "untied." In six pairs of patients symptomatic remissions were induced by hydrocortisone, while in seven pairs mucosal appearances improved with the potent drug. Inert therapy in each pair of patients was uniformly unsuccessful. The number of untied pairs in favour of hydrocortisone was sufficient to establish a significant advantage when recorded on the control charts.

The outcome of treatment in each untied pair was completed on the chart shown in Fig. 1. Information is entered

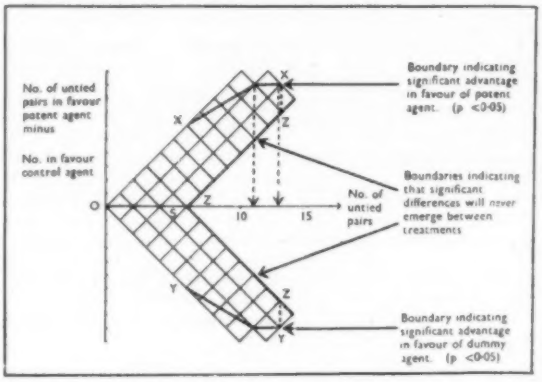
No. of untied pairs in favour potent agent minus
No. in favour control agent
Boundary indicating significant advantage in favour of potent agent. (p <0·05)
Boundaries indicating that significant differences will never emerge between treatments
No. of untied pairs
Boundary indicating significant advantage in favour of dummy agent. (p <0·05)
O
5
10
15
X
Y
Z

FIG. 1.—Sequential analysis chart comparing treatment of granular proctitis with dummy and that with hydrocortisone. Outcome of treatments in untied pairs, starting at point O. For each untied pair favouring hydrocortisone a point is drawn diagonally upwards towards the upper limit of the chart, XX, and for each untied pair favouring inert therapy diagonally downwards towards the lower limit, YY. As soon as one of these limits is intersected the significant advantage of one form of therapy is established. This will occur if 6 of 6, 10 of 11, or 11 of 13 untied pairs favoured one agent. If no significant differences are demonstrated between treatments the control line will oscillate up and down and eventually intersect the inner limits of the chart, ZZ, which might occur after as few as 6 or as many as 13 pairs of dissimilar responses had been entered on the chart. Intersection of these inner limits, ZZ, would indicate that the trial should be abandoned, as no significant advantage for a particular treatment would emerge.

on the chart starting at point O. For each untied pair showing an advantage in favour of hydrocortisone a line is drawn one point diagonally upwards towards the upper limit of the chart XX and for each untied pair in favour of the dummy therapy one point diagonally downwards towards the lower limit YY. If the differences between treatment are great, successive points in favour of the potent remedy rapidly approach the upper limit XX, and once this margin is intersected a significant advantage for potent therapy to the 5% level has been demonstrated.

As will be seen from Fig. 1, this might be possible if six out of six untied pairs favour hydrocortisone when significant differences could be shown after 12 patients had been treated. If one untied pair of patients favoured inert therapy in the course of the investigation the outcome of the trial would be delayed until 10 or 11 untied pairs had favoured hydrocortisone and the upper margin of the chart had been intersected. Finally, if two pairs of patients favoured dummy preparation the outcome of the trial would be delayed until at least 13 untied pairs of patients had been obtained. A similar outcome would occur if dummy treatment was better than potent, when the progression of the line would be downwards to intersect the lower limit YY on the chart. If no significant difference existed between treatments the line would oscillate backwards and forwards and eventually intersect the inner limits of the chart labelled ZZ, which would indicate that even if the maximum number of 13 untied pairs were obtained no significant difference would emerge, indicating the limit to which the trial should be pursued.

The disadvantages of this type of analysis are that the number of tied pairs cannot be predicted precisely and that unless the difference between the agents compared is a great one a significant result will not emerge.

Special charts were used to record the frequency of symptomatic remission and sigmoidoscopic improvement.

The chart illustrating the occurrence of symptomatic remission in the pairs of patients treated is shown in Fig. 2, where it will be seen that remissions were induced in six of six untied pairs treated with hydrocortisone and that the control line favouring this agent rapidly approached the upper limit of the chart, demonstrating a significant advantage in favour of this agent.

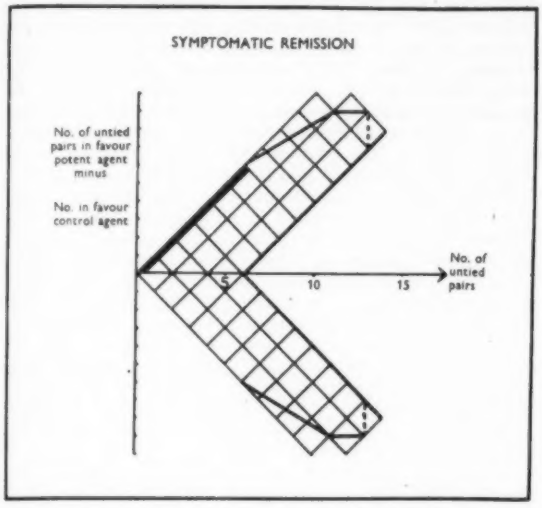

FIG. 2.—Sequential analysis chart illustrating the frequency of symptomatic remission in pairs of patients treated is here shown. As remissions were induced in six or six untied pairs treated with hydrocortisone the control line passed rapidly upwards and intersected the upper limit of the chart, demonstrating a significant advantage for hydrocortisone.

An almost exactly similar chart is shown in Fig. 3, where improvement in mucosal appearance assessed sigmoidoscopically has been recorded. Here again seven of seven untied pairs favoured hydrocortisone, and the control line uninterruptedly approached and intersected the upper limit of the chart, demonstrating again a significant advantage for the potent drug.

Hydrocortisone hemisuccinate sodium therefore was shown to be more effective than a dummy preparation after the small number of 19 treatments had been given and seems a valuable form of therapy for ulcerative colitis, particularly in mild cases where the inflammatory process is confined to the rectum and sigmoid colon. Its use in more severe cases of colitis is being further investigated. In these patients the intravenous administration of 15–30 mg. of propantheline half an hour before the rectal infusion reduces colonic motility overnight and enables the patients with nocturnal diarrhoea to retain the agent overnight. It might also be possible to incorporate the hydrocortisone hemisuccinate sodium in a suppository for use in patients with proctitis. This, too, is being investigated, as this method would prove far more convenient to patients with this disease.

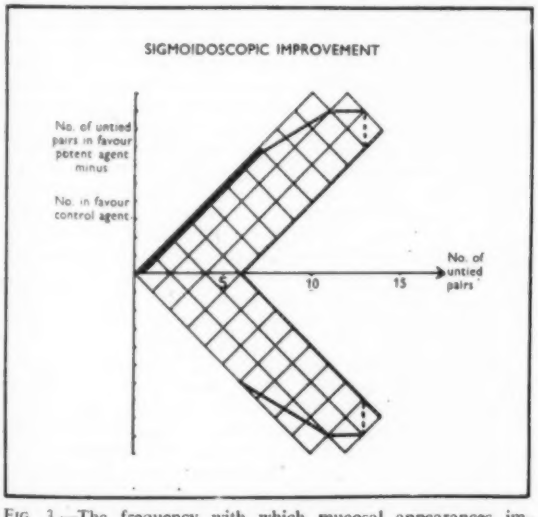

FIG. 3.—The frequency with which mucosal appearances improved sigmoidoscopically is entered on this chart, where again the significant advantage of potent therapy is demonstrated by an uninterrupted progression of the control line upwards to intersect the upper limit of the chart after seven pairs of patients had been treated.

Discussion

The favourable results reported by Truelove in 1956 and 1957 on the treatment of mild cases of colitis by the topical administration of hydrocortisone seemed to merit further inquiry, and for this reason the controlled trial into the value of this mode of treatment was undertaken and has been detailed above.

Truelove in 1956 treated a group of 17 patients with ulcerative colitis on 21 occasions by rectal infusions of a solution of hydrocortisone-free alcohol administered by slow rectal drip, and induced rapid clinical remissions in 14, accompanied in most instances by an improvement in the sigmoidoscopic appearances. A year later he reported a second series of 15 patients with colitis treated on 18 occasions by rectal injection of a solution of the more soluble derivative, hydrocortisone hemisuccinate sodium. Rapid clinical remissions were induced in 11 patients; sigmoidoscopic improvement was observed in every case in remission, accompanied in this instance by reductions in the severity of the inflammatory process judged histologically by serial colonic biopsies and by an improvement in cell morphology as judged by exfoliative studies.

The advantage of potent over dummy therapy has been demonstrated in three ways. Firstly, in the contrasting responses of patients treated in the two ways, where the majority of patients receiving hydrocortisone improved and those receiving dummy treatment worsened. Secondly, in the responses of two patients, serving as their own controls, who received both forms of treatment and who in both cases failed to respond to inert treatment and to undergo remission when potent therapy was given. Finally, by the use of sequential analysis, by which potent therapy was shown to induce symptomatic remission and sigmoidoscopic improvement significantly more commonly than the other form of treatment, the value of the rectal instillation of hydrocortisone hemisuccinate sodium was definitely established.

The new method of restricted sequential analysis designed by Armitage in 1957, modified from the method described by Bross in 1952, proved an extremely satisfactory method of demonstrating the differences, and a significant answer was obtained after 19 treatments had been administered.

Summary

An assessment of the value of rectal instillations of topical hydrocortisone hemisuccinate sodium in patients with ulcerative colitis has been undertaken.

The frequency with which symptomatic remission and sigmoidoscopic improvement were induced has been compared in pairs of patients receiving potent or dummy treatments.

The responses of the groups of patients receiving potent and inert therapy are contrasted. The majority of patients receiving potent hydrocortisone improved and those receiving inert therapy worsened.

In two patients serving as their own controls, dummy treatment failed to induce improvement while hydrocortisone caused a remission to occur.

Finally, comparison by sequential analysis showed that symptomatic remission and improvement in mucosal appearances were significantly more often induced by potent than by inert treatment.

My thanks are due to Glaxo Laboratories, who provided supplies of both potent and inert hydrocortisone for the trial; to Dr. P. Armitage, who designed the sequential analysis chart; and to Professor J. C. Goligher, who performed sigmoidoscopic examinations. I am grateful also to Professor J. C. Goligher, Mr. A. V. Pollock, Mr. G. Smiddy, Mr. E. T. McCartney, Dr. W. S. Suffern, Dr. M. Atkinson, and Mr. D. B. Feather, who referred patients for treatment.

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ANKYLOSING SPONDYLITIS

BY

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In the spring of 1958 a questionary was sent to 343 patients with ankylosing spondylitis who had been seen, and the majority treated, at Westminster Hospital since the war. Answers were received from 209; most of the rest were returned by the Post Office, the present address of those patients being unknown. Many of the patients had been seen and treated while in the armed Forces, and the difficulty in tracing many lay in this fact. In the vast majority of cases, however, where the questionary was sent to the correct address an answer was received within three weeks, demonstrating once again the high degree of co-operation found in our previous study with this group of patients (Hart, Robinson, Allchin, and Maclagan, 1949). Questions were related particularly to the effects of treatment as assessed by the patient himself and the ability to do his work and earn his own living.

Duration of Disease.—Of the 209 who returned their questionaries, 23 had suffered from ankylosing spondylitis since before the onset of the second world war, in 58 the onset lay during 1940–4, in 75 during 1945–9, in 44 during 1950–4; in only 9 had it developed since that date.

Results

Work Capacity.—200 question sheets were returned fully completed. Of these, 21 were from women, 179 from men. This 8.5:1 ratio is an artificial one owing to the high number of Service men seen; it therefore does not reflect the true sex ratio in this disease. Of this number, 160 were working full time, and, if housewives, were doing their full duties in the home. Many stated that in addition to their ordinary duties they worked voluntarily in the evenings, and others did gardening and played games. 40 stated that they were incapable of full duties, but only 9 were incapable of any duties whatsoever. 19 were capable of modified duties and 12 of light or occasional duties. In addition the questionary had been returned by relatives of four patients, all male, who had died: one of amyloidosis, one of coronary thrombosis, one of carcinoma of the pancreas, and one of a neoplasm of uncertain nature. These figures—160 at full work, 19 at modified work, and only 21 capable of little or no duties—are typical of the group as a whole, and similar figures have been reported by Blumberg and Ragan (1956). Although working full time, many commented that the duties in their particular post were not physically hard and some that the post had been selected because of their disability. In four instances a regular paid post had been given up for full-time independent work where self-imposed duties could be varied to avoid the stiffness and discomfort attendant on too little mobility at work. Once again the well-known fact became evident that a stiff spine alone does not cripple, though stiff hips and peripheral joint involvement may.

General Health.—Of 191 patients who answered questions relating to their general health, 36 stated it was excellent, 74 good, 71 "fairly good," and 10 poor. Asked specifically about indigestion, 11 complained of severe recurrent or chronic dyspepsia, 38 of more moderate but annoying symptoms. Radiological investigation in 37 cases had revealed peptic ulcers in 10. Of these 191 cases, therefore, 49, or roughly 25%, have dyspepsia to the point of being a definite and occasionally a major complaint. Although some symptoms were obviously related to or aggravated by therapy, this was clearly not so in all cases. This group of spondylitic dyspeptic patients remains a major therapeutic hazard, for almost all current forms of therapy may aggravate gastro-duodenal symptoms or cause complications. Of other disabilities, the next most common was iritis. Although no specific question was asked and although the eye was not mentioned on the questionary, 35 patients mentioned iridocyclitis when asked for general comments about their health. One was registered as a blind person from this disability. Three patients were under treatment for pulmonary tuberculosis; one had had a thoracoplasty. Vertigo was mentioned by 7, headaches by 4, anaemia by 4, and recurrent bronchitis by only 4, although 8 made major complaints regarding stiffness of the chest wall and inability to breathe deeply.

Analgesics.—To the question, "What medicines have you found to be most helpful for your spondylitis?" 43 answered none, 49 aspirin in some form, 54 compound codeine tables, 56 phenylbutazone, and 9 steroid therapy. This last is a small group, as only a small minority had been offered steroid therapy. No other drug was mentioned more than once.

Radiotherapy

One of the main reasons for the follow-up was to learn what the patients thought of the long-term results of deep *x*-ray therapy and to find out what blood disorders had occurred, if any. The large majority of these patients were treated at Westminster Hospital by Dr. F. M. Allchin, Mr. Tom Prossor, and Dr. Kenneth Newton in the conservative dosage reported by us previously (Hart *et al.*, 1949); only a few treated elsewhere received a total dosage above 1,500 r to any part of the spine, and the majority received under 1,200 r. Of 143 patients who had received therapy to the spine, 114 (80%) stated they had received some benefit, 29 (20%) that they had not. Of those who stated that they had received benefit, 41 (28.7% of all patients treated with deep *x* rays) stated that some benefit still persisted, after follow-up periods varying from 2 months to 17 years since therapy was given; 27 of these 41 patients had received therapy more than four years previously. 30 patients had had symptomatic relief for six months or less, 18 for seven months to five years, 3 for periods over five years, the effect then completely wearing off. In 22 cases details of duration of relief were not adequately given.

While some of this improvement may be psychogenic and reflect the high optimism of the patients as a group, the stories given fall into fairly regular patterns, and suggest more than "therapeutic persuasion." In some cases the question of introduction of a natural remission has to be considered where for many years after therapy the condition appears to have remained largely or completely quiescent. On these figures it seems that 20% of irradiated spondylitics will derive no benefit whatsoever, 20% a temporary symptomatic improvement for a period of up to six months, the remaining 60% some degree of relief for periods varying from seven months to many years.

Discussion

With so many missing returns no conclusions could be drawn as regards mortality and morbidity, though the main reason for failure to return the questionary was the migratory nature of these patients and frequent change of addresses. Nevertheless, of the returns received 80% of the patients were at full work and only 5% capable of no work whatsoever of any sort, the remaining 15% being capable of modified, light, or occasional duties. These figures are the most encouraging we have in the rheumatism unit—far better than those for rheumatoid arthritis. 110 of 191 patients considered their general health good or excellent and only 10 poor.

As regards the most popular of the drugs used it is of interest that aspirin in some form, compound codeine tablets, and phenylbutazone were quoted in almost indentical numbers, the last-named coming top in this poll by the narrow margin of two votes. It has been our impression in the unit for some time that, if tolerated, this drug is the single most useful one for spondylitics at all stages of their painful disease, and Bauer and Ropes (1956) found it more useful in this disease than in rheumatoid arthritis.

The effect of any drug, however, depends on its regular daily administration; its beneficial effects rapidly disappear on stopping it. In contrast, deep *x* rays appear, on this survey, to give some degree of lasting relief in many cases, for 32 of 114 patients (28%) obtained some amelioration of symptoms for over four years. Caution is necessary, however, in interpreting these figures, for a course of deep *x*-ray therapy, like a surgical operation, sticks in the memory as a landmark in the disease course, and subsequent improvement may falsely be attributed to it when, in fact, natural remission has occurred. Improvement, also, is as compared by the patient with pre-treatment symptoms which were severe enough to bring the patient to hospital. One may therefore be comparing symptoms of exacerbation with symptoms of remission, and the therapy given between the two may have been unrelated. A second point to emphasize is that it is impossible on the returns to tell whether symptomatic improvement was great or small; all that can be said is that some measure of symptomatic improvement occurred after therapy.

Wilkinson and Bywaters (1958) found that 43% of 200 irradiated patients required no regular analgesics within a year of completion of therapy, this figure dropping to 22% after a ten-year follow-up. These figures, obtained by clinicians from assessment of analgesic consumption, do not differ very greatly from those obtained by us from an assessment of our patients' own statements.

While I have hitherto been doubtful about the induction of natural remission in this disorder by this form of therapy, there is some indication on these figures that it may occur. The hazards of irradiation are well known, and have latterly received much attention; it is as well to record the reverse side of the coin.

Summary and Conclusions

Question sheets were sent to 343 patients with ankylosing spondylitis, and 209 answers were received. Of these returns, four were from relatives of deceased patients, and five were incomplete. Of the 200 fully completed returns, 179 were from men, 21 from women.

160 (80%) stated that they were working full time; 19 were capable of modified duties, 12 of light or occasional duties; and only 9 were permanently incapable of any work whatsoever.

Of 191 patients who answered questions relating to their general health, 36 stated that it was excellent, 74 good, 71 fairly good, and 10 poor. 11 complained of severe, 38 of moderate but annoying dyspepsia. *X*-ray examination in 37 cases revealed peptic ulcers in 10.

Of 143 patients given deep *x*-ray therapy to the spine, 114 (80%) derived some benefit; 41 (28.7%) claimed some measure of lasting relief, which still continues 2 months to 17 years after treatment. Of these 41 patients 27 were irradiated over four years previously. 30 claimed transient improvement lasting six months or less, 18 improvement for periods of seven months to five years, 3 for more than five years. 32 of 114 (28%) of these patients derived some measure of symptomatic relief for periods exceeding four years.

These results once again emphasize the relatively good prognosis as regards work capabilities in this group of patients and a reasonably satisfactory response to existing forms of therapy.

My thanks are due to Professor J. H. Kellgren and Dr. J. Sharp, of the Rheumatism Research Centre, Manchester University, for their helpful and constructive comments.

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VALUE OF AZACYCLONOL ON CHRONIC SCHIZOPHRENIC PATIENTS

PRELIMINARY OBSERVATIONS

BY

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Azacyclonol hydrochloride ("frenquel") is the gamma isomer of pipradrol hydrochloride ("meratran"), the latter drug being used in this country as an antidepressant agent. Chemically, azacyclonol is α-(4-piperidyl) benzhydrol hydrochloride. Despite its structural resemblance to pipradrol, azacyclonol has been reported to possess different clinical properties inasmuch as it exerts a tranquillizing effect.

Both mescaline and L.S.D.25 have been reported to produce states resembling schizophrenia. Fabing (1955a, 1955b, 1955c), working in the United States, has reported a series of controlled experiments on "normal" volunteers who were each given L.S.D.25. This dose produced a characteristic psychosis with symptoms resembling schizophrenia. The experiment was then repeated, but some of the volunteers were given a course of azacyclonol prior to the administration of the L.S.D.25 and the other volunteers were given control tablets. It was observed that, although the effects of L.S.D.25 began as usual, the more acute symptoms were inhibited in the patients who had been pretreated with azacyclonol. The vivid hallucinatory experiences were absent and some of the group even succeeded in carrying out their normal duties. It would appear from this work that azacyclonol has some blocking effect in experimental psychosis or clinical conditions of disorientation.

The nature of this neurochemical effect is not yet fully understood.

Fabing and Hawkins (1955) have reported on clinical trials with azacyclonol in a series of acute and chronic schizophrenic patients. It appears that azacyclonol affords schizophrenic patients some amelioration of

their symptoms and that it might be a useful addition to the ataractic group of drugs. It was therefore decided to attempt a controlled study of the value of azacyclonol in a group of chronic schizophrenic patients.

Method

Twelve female patients were selected. Their ages varied from 19 to 54 years, with an average of 36.9. The 12 patients were then divided equally into groups known as A and B. The total period of the trial was to be 12 weeks. For the first six weeks the six patients in group A received azacyclonol and the remainder (group B) received identical placebo tablets. The converse of this arrangement was used for the second six weeks.

The experiment was conducted by the usual "double blind" technique. The issue of the tablets was controlled by a member of the male nursing administrative staff who did not know the patients concerned in the trial, and selected the patients for the two groups in a random manner. Until the period of the trial was complete no one else knew which patients were receiving active and which inert material, and all observations were made before the key was broken. During this time none of the patients selected received any other forms of medication, with the exception of one patient, a chronic asthmatic, whose ephedrine, ½ gr. (32 mg.) daily, was continued.

All patients were interviewed prior to the beginning of the trial and their type of schizophrenia was classified as follows: simple, 1; katatonic, 2; hebephrenic, 3; paranoid, 6 (see Table).

The following adjustments were made in ward routine to facilitate observation of the patients. Nurses were instructed to make notes on their patients' behaviour in a special book, with emphasis on the following points: (1) hallucinations, commenting whether patients behaved as if hallucinated or admitted to hallucinatory experiences; (2) degrees of accessibility of patients to friendly approaches by staff or whether hostile, aggressive, or asocial; (3) helpfulness in ward; willingness to partake in household duties and to show initiative with regard to these; (4) response to efforts of staff to keep them tidy in dress and clean in habit; and (5) whether interested in hair styles and responsive to normal use of cosmetics.

Handicraft classes took place in the ward and not in the occupational therapy centre, to maintain continuity in the observation of the patients. The nursing staff assisted at the occupational therapy and accompanied the patients when they were engaged in activities outside the ward—for example, dancing classes, P.T. classes, and walks.

Results

Patient	Classification of Illness	Therapy During Phase 1	Observation During Phase 1	Observation During Phase 2
J. P.	Simple	Azacyclonal	Improved	Deteriorated
M. N.	Hebephrenic	,,	,,	,,
O. S.	,,	,,	No change	No change
T. S.	Paranoid	,,	,,	,,
J. T.	,,	,,	Improved	Maintained improvement
K. B.	,,	,,	Much improved	Deteriorated
M. P.	Katatonic	Placebo	No change	No change
O. R.	Hebephrenic	,,	Slight improvement	Improvement maintained
K. G.	Paranoid	,,	No change	No change
M. B.	,,	,,	Deteriorated	Much improved
M. Bo.	Katatonic	,,	Improved	Improvement maintained
J. K.	Paranoid	,,	Deteriorated	Much improved

Results

Three patients were much improved when receiving azacyclonol. These three patients had several features in common. They were all paranoid schizophrenics, hallucinated, and hostile. They were also asocial, with a tendency to be aggressive if disturbed. Here are summaries of their case histories.

J. K., aged 29. She was suspicious and at times violent, responding to auditory hallucinations and delusions of persecution. On placebo (phase 1) she deteriorated. On azacyclonol she improved and became more accessible. She did not appear so distressed by hallucinations and co-operated in various occupational activities. Her condition deteriorated again after cessation of the trial.

K. B., aged 49. She was sullen, asocial, and suspicious, with no insight. She experienced auditory hallucinations, during which she heard voices of men planning sexual assaults. She had occasional outbursts of physical violence. Her behaviour improved with azacyclonol. She became friendly, co-operative, and helpful with regard to domestic duties. She did not appear to be hallucinated, and denied hallucinatory experiences. Previously she had freely admitted these. Her behaviour deteriorated steadily throughout the placebo phase and the subsequent period after the trial.

M. B., aged 54. At the time chosen for this trial this patient was almost constantly hallucinated. All day long she carried on noisy and interminable conversations with hallucinatory voices. These outbursts often continued far into the night. It was with considerable fortitude that the nursing staff bore with her behaviour and adhered to the rule that nothing other than azacyclonol or placebo should be used during the trial. On azacyclonol her behaviour improved and she became much quieter. She took part in occupational therapy and her hallucinations appeared to diminish in force and intensity.

It will be observed also that two other paranoid schizophrenics displayed no appreciable change throughout the course of the trial. Both of these patients (K. G. and T. S.) had histories of being hallucinated, but did not appear to be so at the time of the trial. Both had well-preserved personalities despite the chronicity of their illnesses, and both had delusions of the paranoid type. It will be appreciated that it is more difficult to observe changes in this type of patient than in the more grossly disintegrated personalities of K. B., M. B., and J. K.

Five further patients showed some improvement in the azacyclonol phase. One of these maintained her improvement later on placebo, but two deteriorated in the placebo phase.

O. R. showed some improvement on placebo in phase 2 but deteriorated after cessation of all tablets.

Discussion

The number of patients selected for this trial was small because it was felt that it would be difficult to assess accurately a larger number of patients. It must be remembered that the nursing staff conducting this trial also had the responsibilities of their routine ward duties.

Conflicting reports have been published referring to the use of azacyclonol. It has been suggested that its major use is for hallucinated patients where the hallucinations are of either schizophrenic or toxic origin (Fabing and Hawkins, 1955).

Later publications, such as reports by Ferguson (1956) and Cohen and Parlour (1956), have shown that higher doses than those used in the trial may be more effective. Recent work with azacyclonol in this hospital has confirmed these observations. It is possible that the principal use of this drug lies as an adjunct to other forms of therapy, when quite noticeable improvement may sometimes be obtained. Fortunately, even in combination, high doses of azacyclonol can be given, as it appears to be completely free from all forms of toxicity and side-effects.

During the early part of the trial detailed blood tests were carried out on all patients, but as no change could be detected this procedure was considered unnecessary and deleted from the programme.

Summary

A study of the effect of azacyclonol on 12 schizophrenic female patients is reported.

The double blind technique was used throughout with the dose standardized at two tablets three times a day (120 mg. daily). In every case all other psychiatric treatment was withdrawn for the duration of the trial.

Substantial improvement was noticed in three patients and some improvement in a further five.

No side-effects were noted.

It would appear that further trials with this drug in disturbed hallucinated patients would be justified and possibly very helpful.

I should like to thank Dr. D. F. Macgregor, medical superintendent of Carlton Hayes Hospital, for his co-operation and assistance with the trial. Also Mr. Mills, senior technician, Mr. Cannings, and other members of the nursing staff. My thanks are also due to Mr. B. A. Weightman, of Riker Laboratories Ltd., who kindly supplied the azacyclonol used in the trial.

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AN AFRICAN'S MENTAL OUTLOOK IN BRITAIN

BY

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"Were all the circumstances, internal and external, scanned closely and weighed accurately it would be seen that there is no accident in madness" (Maudsley, 1879).

To-day, considerable effort is being expended on establishing "scientifically attested knowledge" about how to keep normal persons mentally healthy (Bartlett, 1949). How to maintain the mental health of university students is a serious problem (Parnell, 1951; Gibson, 1953). Indeed, tuberculosis and mental diseases are "the two major medical problems among undergraduates" (*Practitioner*, 1957).

Immigrants suffer mental ill-health more commonly than do the indigenes (Hill, 1943; Crew, 1955). It stands to reason that the mental health of foreign students must be an even graver problem than that of the British-born.

Otis (1955), of Illinois University, has discussed the mental-health problems of foreign students in America. He recommended that "in order to better prepare future students" there was need to analyse problems "met by one's countrymen who have been students abroad." I wish, therefore, to report my own experiences while studying in Britain. It is hoped that this may be of some help to those who are in a position to counsel foreign students.

Writing on colour prejudice in Britain, Richmond (1954) stated that "examples can be cited of psychotic individuals whose behaviour is clearly conditioned by the conflicts that they have experienced through racial prejudice in this country." Sclare (1953) also drew attention to the effect that racial discrimination has on the neurotic pattern seen among American negroes.

If colour prejudice can thus undermine mental health, in what way may the negro student be safeguarded? In presenting my own solution I have in mind what Maxwell (1871) told a meeting of the British Association for the Advancement of Science in 1870: "It was a great step in science when men became convinced that, in order to understand the nature of things, they must begin by asking, not whether a thing is good or bad, noxious or beneficial, but of what kind is it? and how much is there of it?"

Present Investigation

Human beings are "notoriously elusive subjects for objective study and quantitative measurement" (McCalman, 1953). An objective assessment of discriminatory trends in a British city has been made, using a simple, measurable, behavioural quantity—namely, the presence or absence of courtesy in a public utility.

Between November 22, 1954, and November 8, 1955, whenever I paid my fare in any Glasgow Corporation transport I took careful note of whether my fare was accepted with thanks or not with thanks. As a control, I observed whether a European passenger, whose fare was taken just before, or, failing that, just after mine, was thanked or not.

In all, 500 journeys were made. Three types of data were obtained and entered in my diary, each record being made soon after the journey.

Type I—408 cases in which a European fellow passenger and I were both courteously thanked; type II—73 cases in which neither of us was thanked; type III—19 cases in which a European was thanked but I was not. In no case was I thanked but not a near-by Caucasian.

Discussion

It was Lord Lytton (1956) who said that "courtesy is a duty public servants owe to the humblest member of the public." Indeed, the General Manager of Glasgow Corporation Transport Department (1955) reported that his "greatest difficulty is to inculcate amongst the staff a spirit of courtesy and pride of service." Since courtesy is valued so highly in Britain, this social grace is a dependable criterion for a scientific analysis of discriminatory behaviour in this country.

From the above analysis we see that in only 19 cases out of 500 was there acceptable evidence of discrimination. This finding is not statistically significant ($\chi^2 = 0.72$, $P < 0.05$).

The 73 type II cases are noteworthy. Each is potentially fraught with the danger that the negro might think that there was discrimination. If he is not to think so, then comparable discourtesy to Europeans travelling with him has first to be observed. How often, we may well wonder, would such a controlled observation be made in everyday life? Kenneth Little (1947) has said that the negro in Britain may often suspect discrimination and aloofness "where they were never intended." I think that this is true.

What clinical clue, if any, does this conclusion contribute? Weinberg (1955) found that "too frequent and embarrassing uncertainties may lead to inner insecurity, or cause a latent insecurity to become overt." Or, as Hume (1947) put it, sociological factors may undermine mental health by "multiplying precipitating situations." Consequently, the negro student who overestimates prejudice multiplies psycho-social trauma and runs a graver risk of mental breakdown. It is in his own interest that he does not make this mistake.

Admittedly, other investigations may yield a different result; for example, if a criterion other than courtesy is employed. Nevertheless, we may conclude that if there is insight into the difference between real and imagined prejudice the probability is that the threshold of what is unbearable will not be approached. Mental hygiene requires that "environmental difficulties should not be excessive" (Stevenson, 1945). As Bartlett (1949) also said, "there are limits of toleration, both environmental and internal, the persistent passing of which leads to mental trouble."

In education for mental health, correct perception of reality is important (Florence Clothier, 1951). If other

essentials such as financial backing and academic background are satisfactory, a correctly oriented negro student will, like Richmond's (1954) ideal, "not be unaware of the frustrations and tensions which negroes experience, but he will be able to face up to such conflicts, precisely because he has succeeded in achieving, for himself, a measure of status and security. He is less bound by the personal anxiety and inner conflicts which besiege so many of his fellows."

Conclusion and Summary

In Britain to-day the mental health of undergraduates is receiving considerable attention. Since immigrants and those open to racial discrimination are prone to suffer mental ill-health, the mental health of the negro student must be an even graver problem than that of the British-born.

Courtesy shown to me and to European fellow passengers by Glasgow Corporation transport workers has been scientifically analysed. The survey suggests that the negro student may easily overestimate the incidence of racial prejudice.

Now, unfavourable sociological attitudes such as prejudice tend to precipitate mental breakdowns, particularly when they are recurrent. Consequently, adequate insight into the racial environment in Britain will, by ruling out instances of imagined rather than real discrimination, help the African student or a student of other lands to maintain a healthy mental outlook while in this country.

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Medical Memorandum

Congenital Reduplication of Ileo-caecal Valve Presenting as an Acute Intussusception

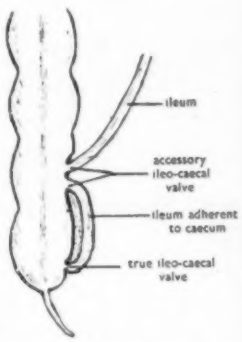
The presence of two separate openings in an intussusception protruding from the anus is unusual enough to be worthy of record. Kolb *et al.* (1956) reported a case of intussusception presenting at the anus with duplication of the caecum, but not of the ileo-caecal valve.

Case Report

A male child aged 19 months was admitted to hospital on July 1, 1955, with a diagnosis of intussusception. He was a firstborn, and was quite well until a week before admission, when he developed abdominal pain and looked ill. Forty-eight hours before admission this pain seemed to become worse, and on the next day he vomited four times and passed loose stools. No blood was seen. On the day of admission he vomited three times, and the mother noticed "that something was protruding from the back passage."

On examination he was a well-nourished but very ill boy, being pale and listless, with a temperature of 99.4° F. (37.4° C.) and a pulse rate of 130. A sausage-shaped tumour was felt in the left iliac fossa and a portion of bowel 5 cm. long was protruding at the anus. On closer examination this was found to have two separate openings, one at the tip and one on the left side. A catheter could be passed into each opening separately for a distance of 15 cm. without difficulty.

At operation the prolapsed bowel was reduced inside the rectum. Laparotomy through a left lower paramedian incision showed a little blood-stained fluid in the peritoneal cavity. The intussusception was felt at the level of the pelvic floor and reduced without difficulty. The appendix and caecum were congested but viable. The terminal ileum was adherent to the ascending colon for 5 cm. above the ileo-caecal valve. As the child was very ill the abdomen was closed rapidly, but, despite emergency measures, he died a few minutes later.



Necropsy (Dr. J. B. Entick-nap).—The terminal ileum and lower right colon were congested. The last 4 cm. of the former was firmly attached to the caecum and opened into it at both ends of this length (see Diagram). The lower opening was a normal valve in position and form. At the upper one the ileum entered the caecal lumen and almost immediately left it again. Histological section at this point showed the muscular walls of caecum and ileum to be continuous and regular, about 6 mm. of the ileum in the fixed and paraffin-embedded specimen forming part of the caecal wall. There was moderately advanced bronchopneumonia of the right upper lobe and an acute tracheobronchitis causing partial collapse of the periphery of both lungs.

Comment

The necropsy findings suggest that the two openings in the bowel prolapsing at the anus were separate ileo-caecal valves, and the regularity of the continuous smooth-muscle layer surrounding them makes it probable that this was a congenital reduplication and not an acquired internal fistula. Gross (1953) reported that 3 out of 702 intussusceptions were due to duplication of the terminal ileum, but neither in his report nor elsewhere have any instances of two valves on a single terminal ileal tube been found.

I thank Mr. R. Parkinson for his help and permission to publish this case.

E. DAYAN, F.R.C.S.,
Surgical Registrar, East Ham Memorial Hospital, London.

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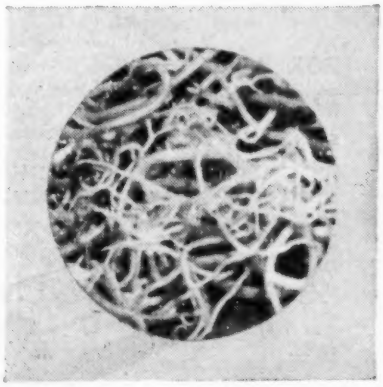

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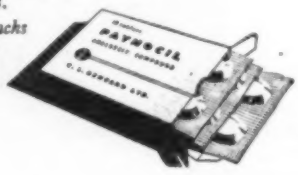

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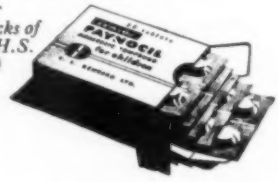

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Reviews

INTERNATIONAL OPHTHALMOLOGY

A Century of International Ophthalmology (1857–1957): Written at the request of the International Council of Ophthalmology. By Sir Stewart Duke-Elder. (Pp. 91; illustrated. 12s. 6d.) London: Henry Kimpton. 1958.

It is indeed appropriate that the task of writing this interesting historical record should have been undertaken by Sir Stewart Duke-Elder, president of the International Council of Ophthalmology, for no one has done more to further the international life of ophthalmology than he. The oldest international medical congress that survives to-day is the International Congress of Ophthalmology, the first meeting of which took place in 1857 in Brussels, the eighteenth meeting being due to take place in the same city in September of this year. If, however, the projected sequence of four-yearly meetings had not been disturbed by wars this year's meeting should have been the twenty-sixth.

This little book of praiseworthy brevity is fascinating to read. The list of chief topics for discussion at each congress shows the trend of ophthalmic thought over the years. The photographs of each successive president add to the attraction. Not the least interesting part of this book is concerned with the reflections of Sir Stewart on international congresses in general. He rightly emphasizes their value, but expresses some dismay at the increasing size of the congresses, which tends to replace the informal give-and-take argument, so valuable from the scientific point of view, by a purely formal discussion or even no discussion at all. He also deplores the increasing cost of the congress, which raises the subscriptions and thus tends to exclude the young ophthalmologist—indeed, the very man who will probably profit most from such meetings.

In Part II of the book Sir Stewart describes the activities of the International Council of Ophthalmology (formed in 1927) and its relation to other sponsored international ophthalmological bodies, and refers briefly to some of its future problems.

This book (as its author suggests) should inspire future generations to maintain the unity and brotherhood of ophthalmologists throughout the world.

T. KEITH LYLE.

INTRODUCTION TO PSYCHOLOGY

Introduction to Psychology. By Ernest R. Hilgard. Under the general editorship of Claude E. Buxton. Second edition. (Pp. 653+xv; illustrated. 55s.) New York: Harcourt, Brace and Co. London: Methuen and Co., Ltd. 1958.

This is the second edition of a very well known and widely used introduction to psychology. There can be no doubt about its excellence, and, though one may upon occasion disagree on points of detail, Hilgard has certainly succeeded in the main in his endeavour to present a fair and widely acceptable review of modern psychology. The new edition has been completely rewritten, and is an improvement on the first in that it sheds to a large extent the slight traces of dogmatism which were so characteristic of the earlier work.

The book is well produced and extremely well illustrated by photographs and diagrams. Indeed, if one were to make a criticism one might say that it is too well produced. The constant changes in size of type, cross-headings, etc., while obviously meant to help the reader, may be found rather distracting. Furthermore, many of the pictures seem quite unnecessary; the fact that Mozart revealed his talent for music at the age of 3 can surely be put over without including a badly reproduced picture of the infant prodigy. This American habit of making learning painless by "visual aids" assumes a level of willingness to learn rather lower than is likely to be found in Great Britain. If half the pictures had been omitted the volume could have been produced much more cheaply; it would also have gained in dignity. However, these criticisms do not alter the fact that this is among the three best introductions to psychology available at the present moment. It will undoubtedly have a wide sale in Britain also.

H. J. EYSENCK.

MEDICAL ANNUAL

The Medical Annual, 1958. A Year Book of Treatment and Practitioners' Index. Edited by Sir Henry Tidy, K.B.E., M.A., M.D.(Oxon.), F.R.C.P., and R. Milnes Walker, M.S.(Lond.), F.R.C.S. (Pp. 580+xl; illustrated. 42s.) Bristol: John Wright and Sons Ltd. Toronto: The Macmillan Company of Canada Ltd. 1958.

Slight changes have been made in this 76th issue of the *Medical Annual*. Hitherto the articles have been arranged in alphabetical order. Now the year's work is reviewed in subsections complete in themselves, which run from Alimentary Diseases to Vital Statistics. This method encourages browsing, which is the attraction of a work of this kind, and there is an excellent index which makes it easy to look up a particular topic. The special articles at the beginning of the review deal with intersexuality, wound infection in operating theatres, dangers arising from the medical use of *x* rays, and the changing emphasis in paediatrics. There are the usual indexes of pharmaceutical and dietetic preparations, surgical appliances, and books of the year. The contributors all seem to be reporting from the active front of medical progress, and the reader of this volume will have a sound idea of recent advances in medicine. The *Medical Annual* is designed to appeal to medical practitioners throughout the Commonwealth, and it seems likely to continue to do so. It is not afraid of describing not merely the useful, as in the reagent strips for urine testing, but the dramatic, as in the extracorporeal circulation whereby the heart can be arrested and laid open for cardiac surgery, and also the bizarre, as in the series of lesions of the male urinary tract. It is something to have learnt that the erythroplasia of Queyrat is not a blood disorder but a lesion of the penis.

L. J. WITTS.

CORONARY HEART DISEASE

Coronary Heart Disease: Angina Pectoris; Myocardial Infarction. By Milton Plotz, M.D., F.A.C.P. Foreword by William Dock, M.D. (Pp. 353+x; illustrated. 90s.) London, Toronto, Melbourne, Sydney, and Wellington: Cassell and Co., Ltd. 1957.

Coronary heart disease, in spite of the intensity of clinical and metabolic and other investigations into its aetiology and natural history, remains one of the obdurate challenges in clinical medicine to-day. As the last important study of these diseases was published eight years ago, the appearance of *Coronary Heart Disease* by Dr. Milton Plotz is of particular interest. He approaches this problem with the concept that this disease is not an inevitable part of senescence, but a malady in which pathogenesis and treatment and prevention have to be studied. The author's interest is so great and his scope so wide that it is hard to find any aspect of coronary heart disease not touched upon and illuminated. The aim of presenting conflicting views in a fair and impartial way has been achieved, but Dr. Plotz has rightly stated his own opinions and practices, which are obviously founded upon a very great experience. To indicate the diversity of themes dealt with in these pages the following among the chapter headings are quoted: geographic and ethnic factors, lipid metabolism, tobacco, ballistocardiography, differential diagnosis, anticoagulant therapy, and surgical and preventive and medico-legal aspects, though this last relates to American law, which differs in material respects from the English.

Any physician who wishes to know the current outlook on any problem relating to coronary disease would be well advised to look herein and, if need be, amplify by study of the bibliography, which is well chosen but derived very largely from North American and British sources.

K. SHIRLEY SMITH.

SYSTEMIC PATHOLOGY

A Text on Systemic Pathology. Volume I. Edited by Otto Saphir, M.D. (Pp. 865+xv; illustrated. $32.00.) New York and London: Grune and Stratton. 1958.

This volume, the first of two, departs from the conventional textbook in its restriction to systemic pathology. Its aim is to provide a work of reference for students and hospital pathologists. Though eleven contributors are listed, Dr. Saphir is personally responsible for most of the book, which includes the cardiovascular, respiratory, urino-genital, and haemopoietic systems. The treatment of these is in general comprehensive and up-to-date, and the text is generously illustrated in black-and-white. Bibliographies are provided at the end of each section.

The success of so ambitious a venture must rest largely upon comprehensiveness and ease of reference, and in these respects it is not above some criticism. For example (p. 460), "Hydronephrosis, Pyelitis and Destructive Pyelonephritis" heads a section in which these conditions are inextricably mixed. It includes, moreover, an illustration of necrotizing papillitis, but the description of the latter appears elsewhere (p. 398) under the main heading of "Nephrosis," without cross-reference to the illustration. If this arrangement is odd, it is even odder to find (p. 169) a note of the endocardial changes found in malignant argentaffinomas in the chapter on congenital heart disease. It seems disproportionate to allocate 28 pages to the subject of hermaphroditism and pseudo-hermaphroditism, interestingly though this is presented, while only 37 pages go to the diseases of arteries, 15 to the testis, and 12 to the spleen. The account given of the last of these omits mention of the storage of cystine in the splenic pulp and other parts of the reticulo-endothelial system in cystinosis. It is also surprising that no distinction is drawn between normocholesterolaemia and hypercholesterolaemia in describing the related storage phenomena in the section on lipidoses. The thymus is ignored both in the chapter on mediastinal pathology and in the treatment of the reticulo-endothelial system. This organ is doubtless relegated to the second volume, but it would seem to deserve some attention in the places indicated.

Despite these criticisms this is a book which can be fruitfully explored upon a wide range of topics, and it can only be regretted that the high and rising prices of this type of work inhibit a wide circulation on our side of the Atlantic.

DOROTHY S. RUSSELL.

CHOOSING DRUGS

Drugs of Choice, 1958–1959. Edited by Walter Modell, M.D. (Pp. 931. 95s.) London: Henry Kimpton. 1958.

There are numerous American textbooks of therapeutics, nearly all written by a team of authorities. Most of them are excellent, their only drawback being their size and price, since it may be doubted whether it is justifiable to purchase such sumptuous volumes on a subject undergoing such continuous and rapid metamorphosis. There are also several American textbooks of applied pharmacology, including Goodman and Gillman, which must be regarded as one of the medical classics of the century. The collaborative work under review is not strictly a textbook of therapeutics nor one of applied pharmacology, but something between the two. It seeks to supply the physician with information about the drug of choice for each therapeutic problem with which he may be confronted. The 35 chapters are concerned with the choice of a diuretic, the choice of an anti-infective agent, the choice of drugs for gastro-intestinal disturbances, and so forth. Each section contains a short discussion of the clinical condition for which the drugs under consideration are used, an account of the several agents commonly employed in its treatment, and the nature of the available data which make one or another the more desirable. At the end of each chapter there is an extensive, but not necessarily complete, alphabetically arranged drug index of the agents commonly used for the disorders under consideration, their dosage, and their proprietary names.

There is a great deal of valuable and wise information in this volume, but it is probable that more conventional textbooks on therapeutics are preferable. There are so many conditions in the treatment of which drugs play little or no part—hyperparathyroidism, for example—which cannot be dealt with satisfactorily by the method adopted, and the treatment of diabetes takes only one and a half of the 931 pages of the book; indeed, the choice of the insulins and hypoglycaemic agents is very inadequately discussed. It is always difficult to obtain a uniform method of presentation in 35 chapters written by 37 contributors, and it must be confessed that the editor of this work has not been entirely successful in this respect.

D. M. DUNLOP.

MODERN DEVELOPMENT OF SURGERY

The Surgeon's Tale. A Story of Modern Surgery. By Robert G. Richardson. (Pp. 256. 25s.) London: George Allen and Unwin Ltd. 1958.

In a modest preface the author of this book tells us that it was written "primarily for the reader with no medical background." He has actually done better than this. He has produced a readable, up-to-date account of the development of surgery during the past hundred years which can be read with advantage by readers who *do* possess such a background.

Recent books on the subject written for laymen have lacked balance and have over-dramatized certain parts of the subject. Here the writing is conscientious, factual, moderate in tone, and more detailed. Though the headings of the chapters may seem popular—"Bugs and Carbolic," "Mainly a Matter of Guts," "Into the Unknown"—the writing is serious and sensible. Yet even with the aid of a glossary (which is provided) it would be difficult for the uninitiated to understand the many operations for hernia or for hydrocephalus which are here described. If, then, we are not certain whether it will appeal to laymen, we have no doubt that medical students and practitioners will alike benefit by reading it, and every surgeon under the age of 50 (and many over that age) will find in it many facts which are new to him. There are some minor errors, but as a whole the book is reliable and accurate and is to be recommended.

ZACHARY COPE.

Volume XXII of the *Cold Spring Harbor Symposia on Quantitative Biology* is devoted to "Population Studies: Animal Ecology and Demography." Subjects discussed include the history of human populations, demographic theory, experimental and theoretical studies of animal populations, the growth of human populations, the ecology of natural populations, the structure of communities, and the population as a unit of evolution. The volume is available from the Biological Laboratory, Cold Spring Harbor, L.I., New York, price $8.

The third edition of *Recent Advances in Oto-laryngology* (438 pp.; J. and A. Churchill, Ltd., 60s.) is the work of F. Boyes Korkis. Previous editions were by R. Scott Stevenson, who contributes a foreword to the present edition. The book has been entirely recast, rewritten, and enlarged. With the exception of some important historical references, the author has confined himself to an evaluation of work published mostly during the last five years. Many useful illustrations are included.

In the second edition of Dr. Sheila Sherlock's *Diseases of the Liver and Biliary System* (pp. 719+xvi; Blackwell Scientific Publications, 57s. 6d.) some careful pruning has made it possible to include new material without adding to the bulk of the book. A chapter has been devoted to jaundice, and the section on jaundice in infancy has been expanded into a more general account of hepatic disease in infancy and childhood. A new classification of hepatic cirrhosis has been included; a number of other additions reflect the advances made in the knowledge of the subject since the first edition appeared in 1955.

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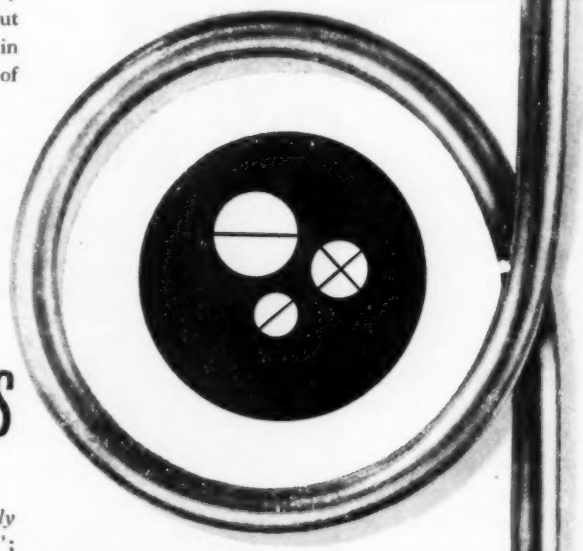

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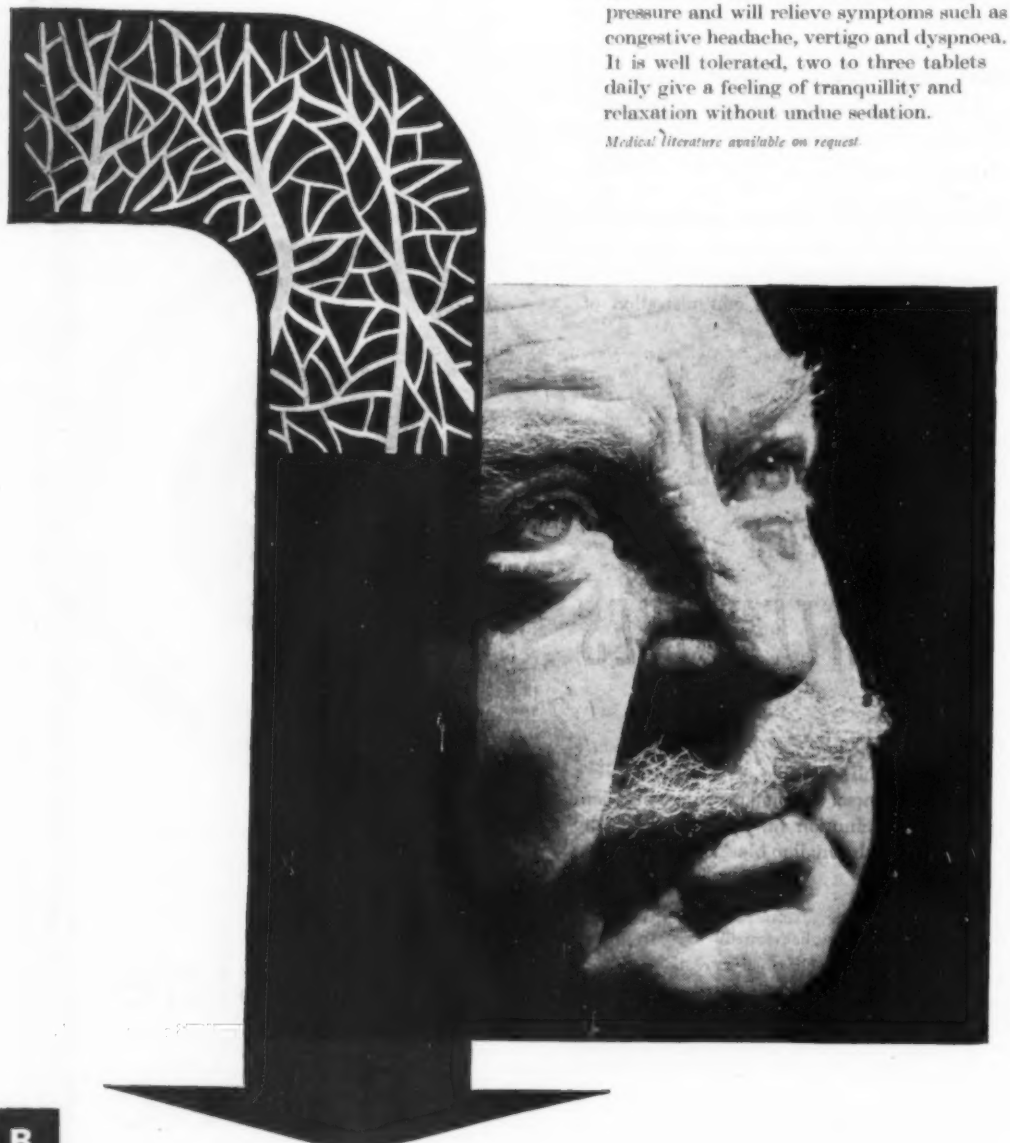

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ALLERGIC ENCEPHALOMYELITIS

Myelinated brain tissue contains some so far unidentified chemical substance which, by subcutaneous injection, can cause severe lesions in the central nervous system. Another component of the nervous tissue can produce polyneuritis and polyradiculitis in experimental animals.[1] The first indication of this phenomenon, and of its relevance to human pathology, was provided by the neuroparalytic accidents of anti-rabic treatment. The use of Freund's adjuvants (paraffin, lanolin, and heat-killed *Mycobacteria*) —which enhance antibody production in known immunological systems—along with the sterile brain tissue, regularly resulted in acute disseminated encephalomyelitis in a wide variety of species. The process is organ-specific but not species-specific. Moreover, since intramuscular injection of the animal's own sterile brain tissue, removed by lobotomy,[2] also caused the disease, experimental support was provided for the postulate of a morbid autoimmunity mechanism.

Perivenous inflammatory infiltrates with a variable degree of perivenous parenchymatous necrosis or demyelination are seen, and histologically the appearances are like those of the human post-exanthematous and post-infectious "myelinoclases." Because of the curious uniformity in the character, and in the time of onset, of human post-infectious encephalomyelitis, independent of the nature of the primary infection, it had earlier been postulated that post-infectious "myelinoclasis" might be a specific disease process,[3] possibly involving sensitization of the nervous tissue.[4] The discovery of experimental allergic encephalomyelitis has therefore suggested strongly that this may be the counterpart of this group of human encephalomyelitides. However, a connexion between exanthematous infections and encephalomyelitis has not yet been successfully shown experimentally.[5] Furthermore, since some workers on human demyelinating disease see no hard-and-fast distinction between acute disseminated encephalomyelitis and multiple sclerosis, it has seriously been postulated that the latter disease also may belong to a group of immunopathological diseases of the nervous system. This thesis was warmly received by many neurologists at the International Congress of Neurological Sciences in Brussels in 1957 in view of the demonstration there, by Y. Uchimura and H. Shiraki,[6] of the striking similarity of human post-rabic vaccinial encephalomyelitis to multiple sclerosis in Japan, where the latter disease is considered to be rare.

The fact that this experimental disease is a non-infective process has been established beyond doubt. For histopathologists it is an education to reflect that this "allergic" encephalomyelitis often far exceeds the most severe of known infective processes in the extent of the visible structural changes which it causes. And in this respect it can be said that the detection of this purely immunopathological process, along with its close counterpart, iso- and auto-allergic thyroiditis, opens up an entirely new field of structural pathology.

Whereas allergic encephalitis was primarily an empirical discovery in experimental pathology and its immunological background remains to be elucidated, experimental allergic thyroiditis is a discovery directly derived from systematic studies in the immunology of tissue substances. E. Witebsky and N. R. Rose[7] found that antisera both to purified thyroglobulin and to unfractionated extracts of thyroid gland contained antibodies which were thyroid-specific and not species-specific. Quantitative studies indicated that the thyroid specific antigens, though closely related, were not identical in all species. When, following partial thyroidectomy, an animal was injected with extracts of its own thyroid tissue along with adjuvants, similar antibodies could be shown to appear in its serum. Witebsky and Rose[8] have shown that these are true antibodies to thyroid protein. Thus, a specific antibody-globulin was produced autogenously in response to an identifiable protein identical with, or very closely related to, the animal's own thyroglobulin. As there was the possibility that denaturation in extraction had rendered thyroglobulin antigenic, the next step was to determine if the circulating antibody had affected the natural substance in the animal's own gland. This led to the discovery of

[1] Waksman, B. H., and Adams, R. D., *J. exp. Med.*, 1955, **102**, 213.
[2] Kabat, E. A., Wolf, A., and Bezer, A. E., ibid., 1949, **89**, 395.
[3] Greenfield, J. G., in Medical Research Council, *A System of Bacteriology in Relation to Medicine*, 1930, **7**, 133, London.
[4] Glanzmann, E. L., *Schweiz. med. Wschr.*, 1927, **57**, 145.
[5] Lumsden, C. E., and Perier, J. O., *Proc. roy. Soc. Med.*, 1958. In press.
[6] Uchimura, Y., and Shiraki, H., *III^e Congrès International de Neuropathologie*, Rapports et Discussions, 1957, page 90, Brussels, *Acta Medica Belgica*.
[7] Witebsky, E., and Rose, N. R., *J. Immunol.*, 1956, **76**, 408 and 417.
[8] *Symposium on Immunopathology*, 1958, Seelisberg. In press.
[9] *Science*, 1958, **127**, 1122.
[10] Witebsky, E., and Steinfeld, J., *Z. Immun.-Forsch.*, 1928, **58**, 271.
[11] Lumsden, C. E., Kabat, E. A., Wolf, A., and Bezer, A. E., *J. exp. Med.*, 1950, **92**, 253.
[12] Thomas, L., Paterson, P. Y., and Smithwick, B., ibid., 1950, **92**, 133.
[13] Kabat, E. A., *VI^e Congrès International de Neurologie*, Rapports et Discussions, 1957, page 31, Brussels, *Acta Medica Belgica*.
[14] Waksman, B. H., ibid., page 48.
[15] Lumsden, C. E., *Proc. roy. Soc. Med.*, 1956, **49**, 148.
[16] *III^e Congrès International de Neuropathologie*, Rapports et Discussions, 1957, page 34, Brussels, *Acta Medica Belgica*.

gross histological changes accompanying the rise of anti-thyroglobulin titre in the circulating blood. The circle of evidence establishing the authenticity of auto-antibodies and of auto-antibody disease would seem to have been successfully closed, and the thyroiditis system must serve as a model for studies of diseases where auto-immunization is postulated.

The present state of the immunology of experimental allergic encephalitis, reviewed recently,[9] is by comparison still unsatisfactory, and there are important differences in detail from thyroiditis. Immunologically, Witebsky's species-nonspecific neural antigen,[10] a lipopolysaccharide, is not itself the encephalitogenic factor. The brain disease occurs much more quickly than the thyroid disease. The antigen seems to be related to the myelin, and each of three types of chemical substance—certain proteolipids, certain proteins, and a phospholipid (? impure)—has encephalitogenic properties, though together they do not account for the total activity of crude brain tissue. Pending identification and purification of an encephalitogenic antigen, studies of the antibodies produced by the injections have been limited to complement-fixing antibodies (tested with crude extracts), and these have shown no clear relation to the disease in the brain[11 12]; nor has either humoral or cellular passive transfer of disease been proved possible.[13] Delayed skin reactions are the only immunological reaction yet found[14] which show any correlation with the development of the disease, and this evidence is so far probably the best favouring the hypothesis of a delayed sensitivity of the tuberculin type as the probable immunological mechanism whereby the brain lesions are produced. The proliferation of the reticular cells in the brain and their maturation to plasma cells strongly support the idea that there is local formation of antibody in the brain itself—though for the same reason it seems this must also occur in the thyroiditis system. Lumsden[15 16] has drawn attention to the localization of the reactive process to the venules in the brain, and has suggested this is due to a combination of a reticular sheath round post-capillary vessels, high permeability of the walls of these vessels, and relative stasis at this level of the brain circulation. The possibility of local liberation of pharmacologically active substances as a secondary phenomenon responsible for the demyelination has been suggested[15 16] as consistent with what is known of other aspects of the pharmacology of the inflammatory response. Further work is therefore needed not only on the immunology but also on the pharmacology and cytology of experimental allergic encephalomyelitis.

UNMARRIED PARENTHOOD

The problems associated with unmarried parenthood have for long vexed administrators and perplexed ecologists. The prevalence of illegitimacy has for many years been greater in Scotland than in England, though the proportion of illegitimate births has fallen in both countries; in 1866, 10.27% of all the children born alive in Scotland were registered as illegitimate, the highest figure ever recorded since the inception of national statistics. The Scottish Registrar-General, in his early reports, was at pains to point out that the causes of illegitimacy in Scotland were essentially different from those prevailing in other European countries and had their origin in different social relationships. He returned to the subject in 1874, finding no correlation between the weight of illegitimacy and the extent of "ignorance or want of instruction" among the people.[1] There were wide variations in incidence from one part of the country to another, and the Registrar thought that the explanation for these must be sought in the habits of the people, their greater or less addiction to "night courtships," the want of moral training, "and to the incontinence of youth, which in some countries, particularly those in which the demand for labourers and workers is great, finds its legitimate channel in marriage, though it may be improvident marriage; while in others prudential check operates so strongly that it leads to that form of non-resident concubinage which results in illegitimate births." G. Seton,[2] writing some ten years later, reiterated that every statistician was "aware that the unrestrained passions which in rural districts result in illegitimate births are in large towns diverted into the channel of barren prostitution." It is certain that illegitimacy was, in general, more prevalent in the rural parts of the Scottish mainland than in other districts; the blackest areas of all were the counties of Banff and Wigtown. In the ten years following 1866 fully 25% of the 1,080 births registered in one Banffshire parish were illegitimate: 59 mothers gave birth to 153 illegitimate children in the course of these ten years, accounting for more than half of the total illegitimacy—2 produced 5 children each; 6, 4 children each; 11, 3 children

[1] Annual Report of the Registrar-General, Scotland, 1874.
[2] Seton, G., *Trans. roy. Soc., Edinb.*, 1883–4, **12**, 117, 619.
[3] Spence, J., Walton, W. S., Mille:, F. J. W., and Court, S. D. M., *A Thousand Families in Newcastle upon Tyne*, 1954, London.
[4] Nisbet, B., at Annual Conference of Scottish Council for the Unmarried Mother and Her Child, 1954.
[5] Greenland, C., *Med. Offr*, 1958, **92**, 265, 281.
[6] *Registrar-General's Decennial Supplement, England and Wales, 1951, Occupational Mortality*, Part II, 1958, Vol. 1, 159, H.M.S.O., London.
[7] League of Nations, *Study on the Legal Position of the Illegitimate Child*, 1939, Geneva.
[8] *The Law in Relation to the Illegitimate Child*, 1958, British Medical Association, London.

each; and 40, 2 children each. A local clergyman who studied the subject about that time came to the conclusion that both religion and education had failed to tackle the problems of illegitimacy: among the causes, he listed drink, seduction under promise of marriage (rarely fulfilled), insufficient supervision of servants, inadequate house accommodation, concubinage, the tolerance of public opinion, and the protection of the "male offender," to some extent, by the existing law.

The matter has continued to command attention in more recent times. J. Spence and his co-workers[3] found that less than half of the illegitimate children in their Newcastle series were first babies; many of the second and third infants were born to parents living in established, if unofficial, families. In Kilmarnock, B. Nisbet[4] found that 30% of the mothers of illegitimate children were cohabiting. Many of these families are living under extremely bad environmental conditions, often in condemned property, with little prospect of getting a better house—cohabitators do not rank high in official housing lists. In recent studies of unmarried parenthood, based largely on the case records of the National Council for the Unmarried Mother and Her Child (rather biased and incomplete material, as he points out), C. Greenland[5] concluded that a combination of factors, such as residence away from home, and certain types of employment, particularly domestic and clerical work and nursing, appear to be associated with an increased risk of conception in young unmarried women. In many cases the mother had applied to the Council for general information and advice; in 13% she wanted advice about an affiliation order; in 9% she was seeking employment and a home; while in 8% she was concerned primarily with ways and means of keeping the child. Greenland found that men under 20 years of age, married men, or members of armed Forces were often the fathers of illegitimate babies, but his findings did not lend support to "theories which regard putative fathers as a homogeneous group having certain psychological features in common."

The welfare of the illegitimate child has long given cause for anxiety. At one time the official attitude to illegitimacy was more concerned with possible repercussions on the poor rate than with the welfare of the child. From 1868 onwards the officers of the Board of Supervision urged parochial boards in Scotland to offer only indoor relief to the mothers of illegitimate children, hoping by this course of action to reduce the burden of pauper illegitimacy, though the refusal of outdoor relief in these cases often led to the death of the children. It has been the general experience that the prospects of survival of the illegitimate child are much less favourable than those of the legitimate. Recently the Registrar-General[6] has pointed out that the mortality rates of illegitimate infants are much less accurate than those of the legitimate infants, partly because a proportion of the infants who are registered at birth as illegitimate and subsequently die are not recorded as illegitimate at death registration: it is probable that this has the effect of under-estimating the infant mortality of illegitimate children by about 16%. In 1930–2 the calculated illegitimate infant mortality rate was 79% higher than the legitimate rate; by 1949–53 the excess had fallen to 36% and there had been as well a substantial decline over that period in the mortality of infants in each social class. But, apart from considerations of mortality, the illegitimate child usually starts life with serious handicaps, social, emotional, moral, and legal. The League of Nations study[7] of the legal position of the illegitimate child and, more recently, the joint report of the British Medical Association and the Magistrates' Association[8] were agreed that changes in the law were urgently necessary to protect the unmarried mother and her child, and the time seems to be ripe for further action.

BLOOD GROUPS OF MUMMIES

The considerable success achieved by blood-grouping methods in the classification of living human populations has led from time to time to attempts to determine the blood groups of human bones and other tissues obtained from archaeological excavations. Most of the experiments have been limited to the antigens of the ABO system, and it is still exceedingly doubtful whether it will ever be possible to detect the antigens of the other systems in post-mortem material which has not been specially preserved. It is of course impossible to obtain intact red cells from archaeological material, and tests must therefore depend on the inhibition of the grouping sera by samples of the tissues or by extracts or preparations from them. The earliest experiments were those of W. C. Boyd and L. G. Boyd,[1] who performed inhibition tests with muscle tissues from Egyptian and American Indian mummies. Since then methods have been somewhat refined, though no great advances have been made; P. B. Candela[2] appears to have been the first to carry out tests on ground samples of bone, a substance much more widely available than muscle tissue. The literature of archaeological blood grouping up to 1953 has been reviewed by A. E. Mourant.[3]

[1] Boyd, W. C., and Boyd, Lyle G., *Proc. Soc. exp. Biol. (N.Y.)*, 1934, **31**, 671.
[2] Candela, P. B., *Amer. J. Phys. Anthrop.*, 1936, **21**, 429.
[3] Mourant, A. E., *The Distribution of the Human Blood Groups*, 1954, Oxford.

The results of tests on series of ancient remains have proved generally consistent with those on the corresponding living populations, but have often shown an excess frequency of group AB above that required for genetical equilibrium. It thus appears probable that while, taken on a population basis, the results do give some indication of genetical constitution, most if not all series include some false positives. This is not surprising, since all the specimens tested must contain bacteria. Bacterial contamination is already known to give rise for various reasons to errors in the testing even of red cells only a few days or weeks old. Some such results depend upon the Thomsen phenomenon, which is due to the development of an antigen not closely related to the blood groups. This causes "false" positive agglutination and hence would give rise to false results in the detection of blood-group antigens by inhibition methods. On the other hand some bacterial polysaccharides are closely related biochemically and even immunologically to the blood-group substances and so might be expected to cause inhibition simulating that due to the blood-group antigens.

If blood-group tests are to be used for archaeological purposes, and if the results are to command any confidence, it is clear that existing techniques need to be refined considerably, or new methods developed. In either case the methods, before being applied to ancient specimens, must be shown to give correct results with recent cadaver material of which the blood group is known. It may be that the blood-group antigens are too unstable on the one hand or too similar to bacterial polysaccharides on the other for a standard of accuracy ever to be reached comparable with that attained in the testing of living persons; but if reliable results could be obtained they would be of such great value to archaeologists that it is important that renewed efforts should be made to improve the methods of testing.

The news is therefore welcome that a blood-grouping laboratory for these purposes has been set up at the British Museum (Natural History). Work is being carried out by Mrs. Madeleine Smith in the Anthropology Section, of which Dr. K. P. Oakley has charge. The first object of the laboratory is the development and critical assessment of new and more accurate testing methods. It is proposed, however, to undertake almost immediately the testing both of a certain amount of "mummified" material (for example, from the dry soils of Peru) and of a selection of bones of ancient Etruscans, which have been preserved under damper and presumably less favourable conditions. In the long run there is little doubt that mummified material will yield valuable if not completely accurate results; such results would of themselves fully justify the establishment of the laboratory. If in addition reliable methods can be developed for the testing of bones preserved under moist conditions a most important addition will have been made to the scope of archaeology, and a great contribution to the possibility of correlating ancient populations with those of the present day.

GOITROUS HYPOTHYROIDISM

Recent advances in knowledge of thyroid function have emphasized the diagnostic significance of a palpable thyroid gland in a hypothyroid subject, whether baby, child, or adult. The gland itself may be soft or hard, smooth or nodular, small or large, but from its enlargement certain conclusions may be drawn: that the thyroid is subject to some difficulty in producing thyroxine and triiodothyronine, that this difficulty has been present for some time, and that the deficient output of thyroid hormones has resulted not only in the clinical state of hypothyroidism but also in an increased production of the thyrotrophic hormone T.S.H. in the endeavour to stimulate output of thyroxine. This attempt is unsuccessful, and the best that T.S.H. can achieve in this situation is an enlargement of the gland due to hyperplasia.

The thyroid gland is not as a rule well palpated by medical students or by young clinicians. The correct method of examination remains a matter of opinion, but the method usually taught of standing behind the sitting patient and blindly palpating with both hands has little but custom to commend it. Few right-handed clinicians have a left hand as sensitive as the right (the trouble, as Trotter used to explain, with some of us is that we have two left hands), and everyone uses either hand more expertly when aided by direct vision. The methods of standing alongside (to the right if right-handed) the sitting patient and palpating with one hand appears to achieve better results when used by those clinicians not yet wedded to the older method. In hypothyroid children in whom no gland can be palpated in the usual situation the possibility of dysgenesis[1] (imperfect descent) is worth remembering, and the examining fingers should explore the neck on both sides below the jaw.

Further conclusions can be drawn from the nature of the enlarged gland in hypothyroid subjects when the patient and his environment are considered. The discovery of a small, even tiny, gland in a baby with cretinism or in a child with hypothyroidism suggests an inborn defect of thyroxine synthesis; this is even more firmly indicated when the gland is large and nodular and the patient older. The enlarging gland in the thyrotoxic patient treated by antithyroid drugs shows that the patient is moving over to hypothyroidism. The hard and enlarged gland of autoimmunizing thyroiditis is often associated with myxoedema in women.

But in the present state of our knowledge we must not conclude that, because the thyroid gland is atrophic and impalpable in the presence of hypothyroidism, the gland has therefore not been the seat of similar inborn defects or of pathological processes. It is easy to conceive that

[1] McGirr, E. M., and Hutchison, J. H., *J. clin. Endocr.*, 1955, **15**, 668.
[2] Wyngaarden, J. B., Stanbury, J. B., and Rapp, B., *Endocrinology*, 1953, **52**, 568.
[3] Astwood, E. B., *Ann. N.Y. Acad. Sci.*, 1949, **50**, 419.
[4] Mosier, H. D., Blizzard, R. M., and Wilkins, L., *Pediatrics*, 1958, **21**, 248.
[5] Stanbury, J. B., and Hedge, A. N., *J. clin. Endocr.*, 1950, **10**, 1471.
[6] —— Kassenaar, A. A. H., Meijer, J. W. A., and Terpstra, J., ibid., 1955, **15**, 1216.
[7] Stanbury, J. B., Ohela, K., and Pitt-Rivers, R., ibid., 1955, **15**, 54.

a gland destroyed by chronic thyroiditis is incapable of response to T.S.H., and remains shrunken and atrophic; and there is now good evidence that myxoedema is often, if not always, the result of such a process. It is also possible that the foetal thyroid gland, as the result of some inborn enzymatic defect, may also fail to respond to T.S.H.

One group of antithyroid drugs such as potassium perchlorate and thiocyanate act by preventing the uptake of iodide by the gland,[2] and they are used also in the investigation of thyroid function to procure the discharge of iodine unbound to tyrosine from the gland. Another group, the thiocarbamides such as methyl thiouracil and carbimazole, prevent the iodination of tyrosine[3] (the second step in the synthesis of thyroxine). Three types of congenital defect in the synthesis of thyroxine have now been identified.[4] The first defect occurs at the stage of iodination of tyrosine[5] (the stage at which the thiocarbamides have their action). The second defect is due to a failure of deiodination of the iodotyrosines, presumably associated with a failure of the enzyme dehalogenase.[6] And the third is a partial inability to form thyroxine and triiodothyronine from the iodotyrosines.[7] No drugs are known to interfere with the late stages of thyroxine synthesis at which the second and third of these congenital defects declare themselves. Hypothyroidism which is due to the use of antithyroid drugs requires the temporary cessation of therapy. Hypothyroidism which is due either to congenital defects in thyroxine synthesis or to chronic thyroiditis requires lifelong thyroid therapy—sufficient for the needs of the body, sufficient to suppress the formation of T.S.H., and sufficient to put the overactive or pathological gland at rest.

IMMUNIZATION AGAINST DIPHTHERIA

The proportion of children in different parts of the country immunized against diphtheria varies widely. Though precise figures are not readily available, it seems to range from under 30% to over 70% in England and Wales, and to average about 70% in Scotland. The present outbreaks in Essex and London,[1] though small by the standards of 20 years ago, are a reminder that a high state of immunization is the surest barrier to the epidemic spread of the disease. The number of children immunized in England and Wales against diphtheria in the three years 1955–7 was 525,125, 567,989, and 546,776, respectively. The percentage of children who may be regarded as remaining protected—that is, children who had a course of immunization, primary or booster, during the preceding five years—for the years 1953–7 was 48, 48, 49, 49, and 48. In Scotland it was about 70%. Though the percentage throughout the country varies from place to place, it varies only slightly from year to year in any area. In a speech he made last week Dr. J. A. Stirling, the new president of the Society of Medical Officers of Health, wisely urged his colleagues to keep parents well informed about the necessity of having their children immunized.

[1] *Brit. med. J.*, 1958, **2**, 1051.

In England and Wales in 1956 there were 11 cases of diphtheria among the immunized with 1 death, and 40 cases among the non-immunized with 2 deaths. In 1955 there were 34 cases among the immunized with no deaths, and 120 among the non-immunized with 13 deaths. In Scotland, during the nine years 1949–57 there were 151 confirmed cases of diphtheria among the immunized children, with no deaths; among the non-immunized children there were 665 confirmed cases, with 35 deaths.

The number of notifications of diphtheria fell rapidly after the widespread introduction of immunization, from an annual average of about 55,000 in 1933–42 to 40 in 1957, while the number of deaths fell from an annual average of 2,783 in 1933–42 to six in 1957. The distribution of cases was sporadic, and the largest annual number of cases in local authority areas in 1955 was 19 in Uttoxeter R.D., 17 in Kingston-upon-Hull C.B., and 14 in West Ham C.B. Kingston-upon-Hull had the largest annual total in 1956 and 1957, with 7 and 6 cases respectively. It is interesting to note that, though full swabbing of family, school, and other contacts was performed in most areas where cases occurred, in only a few instances were carriers revealed; the source of infection usually remained unknown. Past experience has shown that in school communities where immunization rates are low diphtheria has only to be introduced to spread rapidly. It is at school entry that an opportunity exists to raise the number of immunized children in the community.

B_{12} ASSAYS IN MEGALOBLASTIC ANAEMIA

Uncomplicated vitamin-B_{12} deficiency in man frequently gives rise to megaloblastic anaemia, which can be differentiated from that seen in folic-acid deficiency or in scurvy[1 2] by the fact that it is cured by treatment with vitamin B_{12}. However, the lingual and neurological lesions caused by deficiency of vitamin B_{12} are sometimes found in patients who are not anaemic,[3 4 5] and deficiency of B_{12} and folic acid may occur together in patients with intestinal malabsorption syndrome. In such patients it may be impossible to diagnose deficiency of vitamin B_{12} by clinical and haematological methods alone.

However, deficiency of B_{12} can be detected in these patients by assaying the amount of it in the serum by the use of micro-organisms, of which *Euglena gracilis*[6 7]

[1] Jandl, J. H., and Gabuzda, G. J., *Proc. Soc. exp. Biol. (N.Y.)*, 1953, **84**, 452.
[2] Brown, A., *Brit. J. Haemat.*, 1955, **1**, 345.
[3] Badenoch, J., *Proc. roy. Soc. Med.*, 1954, **47**, 426.
[4] Arias, I. M., Apt, L., and Pollycove, M., *New Engl. J. Med.*, 1955, **253**, 1005.
[5] Adams, J. F., *Lancet*, 1957, **1**, 1120.
[6] Ross, G. I. M., *J. clin. Path.*, 1952, **5**, 250.
[7] Hutner, S. H., Bach, M. K., and Ross, G. I. M., *J. Protozool.*, 1956, **3**, 101.
[8] Rosenthal, H. L., and Sarett, H. P., *J. biol. Chem.*, 1952, **199**, 433.
[9] Spray, G. H., *Clin. Sci.*, 1955, **14**, 661.
[10] Mollin, D. L., and Ross, G. I. M., *Proc. roy. Soc. Med.*, 1954, **47**, 428.
[11] —— —— in *Vitamin B_{12} und Intrinsic Factor*. 1. Europäisches Symposion, Hamburg, 1956, edited by H. C. Heinrich, p. 413. Ferdinand Enke Verlag, Stuttgart.
[12] Lear, A. A., Harris, J. W., Castle, W. B., and Fleming, E. M., *J. Lab. clin. Med.*, 1954, **44**, 715.
[13] Girdwood, R. H., *Quart. J. Med.*, 1956, **25**, 87.
[14] Meynell, M. J., Cooke, W. T., Cox, E. V., and Gaddie, R., *Lancet*, 1957, **1**, 901.
[15] Spray, G. H., and Witts, L. J., *Brit. med. J.*, 1958, **1**, 295.
[16] Gardner, F. H., *New Engl. J. Med.*, 1958, **258**, 791.
[17] Tasker, P. W. G., Mollin, D. L., and Berriman, H., *Brit. J. Haemat.*, 1958, **4**, 167.

and *Lactobacillus leichmannii*[8 9] are the best known. Measured in this way, the B_{12} concentration in the serum of patients with Addisonian pernicious anaemia[10–15] is always lower than in normal subjects. While the B_{12} concentration in the serum of normal subjects ranges from 140 to 900 $\mu\mu$g. per ml., most patients with Addisonian pernicious anaemia have levels of less than 80 $\mu\mu$g. per ml. However, some control subjects may have levels as low as 100 $\mu\mu$g. per ml. and a few non-anaemic patients with Addisonian pernicious anaemia have levels up to 110 $\mu\mu$g. per ml. On the other hand, all patients with subacute combined degeneration of the cord, even when they have no anaemia, have little or no measurable B_{12} in their serum with the Euglena assay.[10 11] The diagnostic value of such an estimation is clear. In addition, this observation suggests that subacute combined degeneration does not develop until the tissues are almost completely depleted of B_{12}, and furthermore that the megaloblastic anaemia in pernicious anaemia may not be due solely to deficiency of B_{12}.

The incidence of B_{12} deficiency may also be accurately assessed in other megaloblastic anaemias by this method. For instance, in patients with megaloblastic anaemia associated with gastrectomy and with anatomical lesions of the small intestine the B_{12} concentrations in the serum are almost always subnormal, the levels being similar to those seen in Addisonian pernicious anaemia. Deficiency of folic acid rarely occurs in these patients, for they usually respond completely to treatment with vitamin B_{12}. Subnormal levels of B_{12} in the serum are also common in tropical sprue[16] and in "tropical megaloblastic anaemia,"[17] but in these conditions they are more frequently associated with deficiency of folic acid, for the haematological responses to treatment with B_{12} are slower and less complete. Subnormal levels are also found in about 50% of the patients with idiopathic steatorrhoea,[10 14] and in one-third of these patients the levels are as low as in pernicious anaemia, being less than 100 $\mu\mu$g. per ml. However, in such patients the B_{12} deficiency is invariably associated with folic-acid deficiency, for none of these patients appear to respond completely to treatment with B_{12} alone. Subnormal levels of B_{12} in the serum are less frequent in megaloblastic anaemia of pregnancy,[11–15] and in most patients the concentrations are normal.

While the evidence suggests that a B_{12} concentration in the serum of less than 80 $\mu\mu$g. per ml. indicates clinical B_{12} deficiency, serum levels between 80 and 120 $\mu\mu$g. per ml. have been found occasionally in patients whose tissue stores of B_{12} were normal.[11] Though such findings are very rare, they suggest that borderline levels of serum B_{12} should be interpreted with caution.

ADVERTISING DRUGS

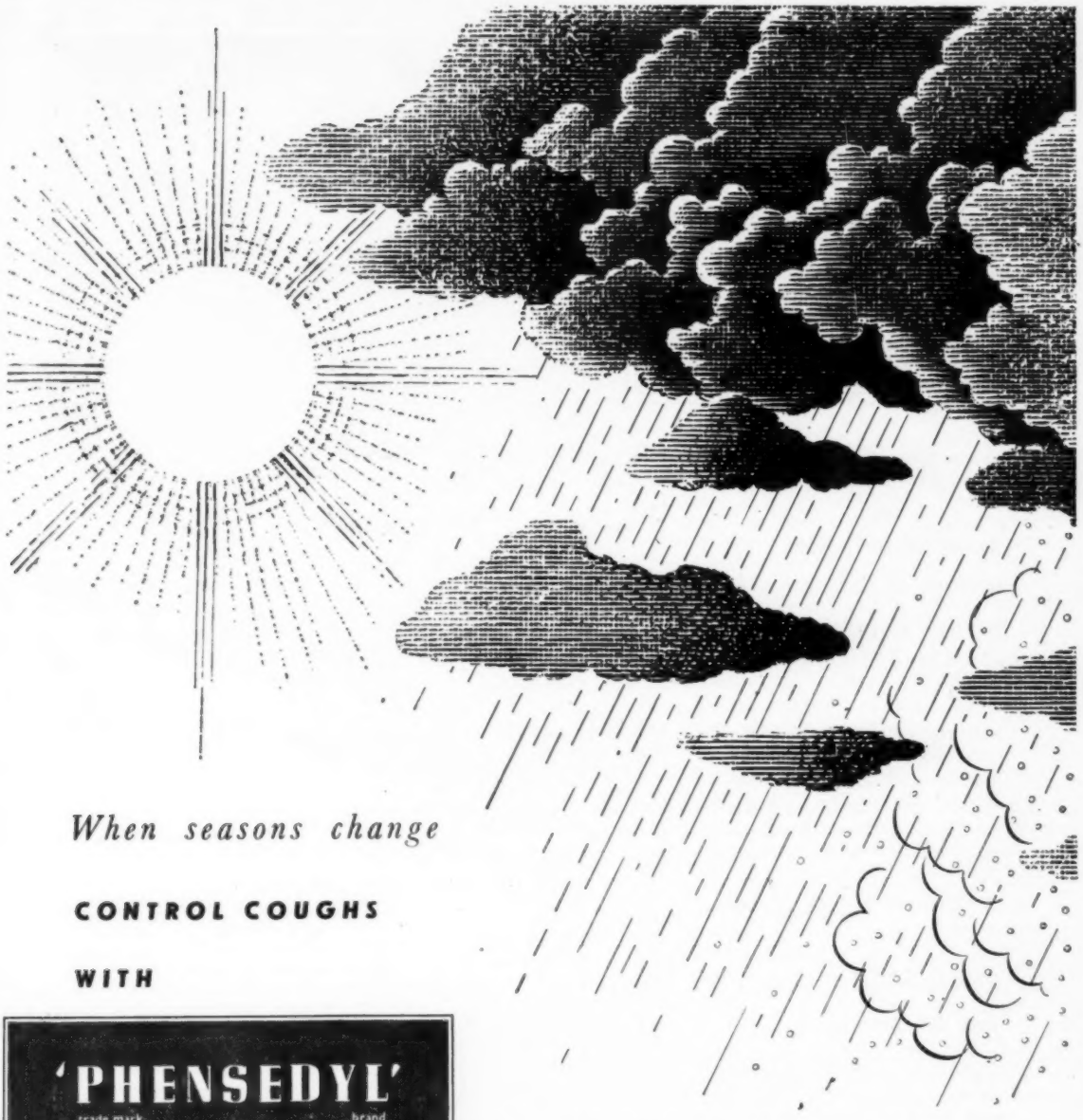
"You can count the number of useful drugs on the fingers of your two hands" one well-known physician used to say to his students little more than thirty years ago. Since then there has been a revolution in the drug treatment of disease. The revolution is still on. The brilliance of the bacteriologist, chemist, and pharmacologist, combined with the energy and resourcefulness of the pharmaceutical industry, has let loose a flood of new and powerful remedies to be used by doctors for the benefit of patients. Politicians and administrators moan about the cost of this to the National Health Service. At one time the size of the national drug bill was attributed to unrestricted and free access to the simple remedies and dressings in the chemist's shop. Then the blame fell on the pharmaceutical industry for high-pressure salesmanship of remedies, and combinations of remedies, the cost of which was regarded as excessive. No one has been entirely free from blame, least of all the politicians who encouraged the whole population of the United Kingdom in the belief they could take what they wanted out of the chemist's shop without having to pay for it. But without the pharmaceutical industry modern medicine would be powerless to do good with the drugs modern science provides for it, drugs discovered often enough in the laboratories of the industry itself. Information about these drugs reaches the practising doctor in a number of ways, and elsewhere in this issue Dr. Audrey Baker describes the results of her inquiry into the value set by doctors on the information given by pharmaceutical houses through the post, by medical representatives, and in the advertisement columns of medical journals. Some 90% read the advertisements for drugs in medical journals—64% often or always, and 26% seldom. That 80% preferred to get their information on drugs by discussion with firms' representatives suggests that the industry as a whole might look more critically at the type of copy their agents send to the medical press.

What is of special interest to us is Dr. Baker's conclusion that there is "a *British Medical Journal* readership of between 80% and 90%," throughout Great Britain, a record far outstripping that of all other medical periodicals. This is gratifying to us and, we may assume, to the growing number of firms aware of the value of advertising their wares to the *B.M.J.'s* readers.

NOBEL PRIZE FOR CAMBRIDGE BIOCHEMIST

The award of the Nobel Prize for Chemistry to Dr. F. Sanger, F.R.S., is in recognition of his outstanding work in analysing the structure of the insulin molecule. The work took about ten years to complete and was carried out with his colleagues in the Biochemistry Department at Cambridge University during 1945–55. Now aged 40, Dr. Sanger was elected a Fellow of the Royal Society four years ago. At the time this work was completed the insulin molecule was the largest protein molecule to have had its chemical structure elucidated. This great achievement was an essential preliminary to any chemical synthesis of insulin as well as of analogues which may be easier to administer in clinical practice.

We record with regret the death on October 24 of Sir John Megaw, formerly professor of tropical medicine at the Calcutta School of Tropical Medicine and Director-General of the Indian Medical Service from 1930–33.



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The suitability of a patient for treatment with Rastinon tablets is readily assessed in the diabetic clinic and once stabilised no difficulties have been experienced in controlling the patient. An acute intercurrent infection may necessitate a temporary return to insulin therapy.

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Once stabilised, from one to three tablets a day are normally all that is required to replace the insulin with its concomitant syringe, needles, swabs, and often nursing assistance as well. During the period of stabilisation it has been found that generally from four to eight tablets on the first day, three to six on the second and three to five on the third are sufficient.

The daily amount should be divided into two or three doses and taken during or after meals with a little fluid. Higher doses are not usually more effective and are not recommended as they may occasionally cause hypoglycaemic reactions. The normal regime of urine examination and dietary control remains necessary.

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PACKS

Bottles of 100 and 500 tablets—each tablet contains 0.5 G. N-Butyl-N'-toluene-p-sulphonylurea (tolbutamide). The basic cost to the N.H.S. of a week's treatment is on average between 3/6d. and 5/3d.

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Further information on request.

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Drug Treatment of Disease

SEDATIVES AND TRANQUILLIZERS: PART II*

BY

WILLIAM SARGANT, F.R.C.P.

Physician in Charge of the Department of Psychological Medicine, St. Thomas's Hospital

Tranquillizers

In recent years over twenty so-called tranquillizers have been marketed by drug manufacturers to replace or to reinforce the older types of sedatives already discussed. Unfortunately some of these drugs have been offered to general practitioners long before they have been properly tested in Great Britain, and false claims and even some disasters have occurred. We have seen, for instance, the spate of suicides by depressive patients following the unwise advocacy of reserpine as a tranquillizer for general use and in the treatment of hypertension before this fatal complication of treatment had been fully realized. Many cases of jaundice likewise followed the enthusiastic claims made for chlorpromazine long before most British psychiatrists had had any real opportunity to test it out and to find its potential advantages and dangers. Again, it is now known that chlorpromazine can greatly increase depression in an already depressed person (though perhaps not to the same extent as reserpine), with the consequent risk of suicide. It is thus inadvisable to try out new tranquillizers in general practice until they have been thoroughly tested in Great Britain, and tested in circumstances which will prevent the disasters that have happened in recent years.

The writer has, so far, been able to try out only some of these new tranquillizers in a way which justifies their detailed discussion in an article of this nature. Others may be useful, but some have proved of little use at all, and should never have been put on the market or advertised for general use.

Chlorpromazine

This drug unfortunately produces jaundice in some patients, but the benefit it gives often makes this a worthwhile risk if the patients are properly selected for it. It is of far greater value in the sedative treatment of the psychotic patient in hospital than the neurotic patient outside. But there is now some evidence that chlorpromazine, if given in sufficiently large doses (200–400 mg. a day), may abort the development of acute schizophrenic illnesses in some of those persons predisposed to them. General practitioners may find it advisable to give this drug immediately to patients in the very earliest phases of the illness and while awaiting, for instance, the taking of further expert advice on future treatment. Since its introduction in psychiatry, this drug has also enabled many schizophrenic patients to be treated much more speedily than previously, and some can now stay on as out-patients instead of having to go into hospital for insulin-coma and other treatments. Even when other treatments, such as full or modified insulin, E.C.T., and leucotomy also have to be used, chlorpromazine seems to be a drug of considerable value as a maintenance treatment, tending to prevent relapses. However, quite large doses are generally necessary, doses which can, in fact, markedly aggravate other neurotic and psychotic conditions. Indeed, schizophrenics may need to be given initially up to 1,000 mg. a day, and maintenance doses of 150–400 mg. a day may also be necessary later on. At present we do not yet know how long these large doses have to be kept up; but relapses often occur within a month of the patient being taken off the drug even after prolonged use.

There are also many elderly senile patients, suffering particularly from agitation, in whom ordinary sedatives produce confusion and increasing upset of memory. Such patients are often greatly helped by the use of chlorpromazine in lower doses—say, 100–200 mg. a day. By damping down their agitation it may enable them to be nursed at home rather than in hospital. In ordinary neuroses chlorpromazine should be given much more hesitantly. Doses in the region of 100 mg. a day can help some patients with anxiety and depression, but the administering of this drug alone in cases of depression can increase the symptoms, sometimes to the point of suicide, and general practitioners must always be on their guard against this. Anxiety states, anxiety hysteria, and obsessional states are really little helped by this drug, and the barbiturates will be found much cheaper and much more effective. Chlorpromazine, however, may be used to reinforce small doses of barbiturates, and to prevent larger doses producing undesirable states of barbiturate addiction.

Several substitutes and equivalents have been produced for chlorpromazine, some of them claiming that jaundice is avoided as a complication of their use. These may be tried where jaundice has occurred, but whether they are as effective as chlorpromazine is as yet far from certain.

Reserpine

This drug has also had a recent vogue in the sedative treatment of anxiety states and in schizophrenia. Some excellent results have been reported in schizophrenic illnesses when the dose is pushed to as high as 8–10 mg. a day, and a maintenance dose of around 3–6 mg. a day is used later. But there are many undesirable features attaching to the use of this drug. Suicidal depressions are very common, and it is doubtful whether much better results are obtained with reserpine than with the skilled use of chlorpromazine in a proper high dosage. Smaller doses of reserpine (1–2 mg. a day) can, however, be given to supplement larger doses of chlorpromazine.

Some tension states are also undoubtedly helped by much smaller doses of reserpine—about 0.25 mg. three times a day. But it is difficult to delimit these, and one should try to use every other drug first, because of the drug's liability to produce such severe depressive reactions. The physician should be especially careful in treating anyone who has a prior history of a neurotic or psychotic attack of depression.

Meprobamate

This expensive sedative has had a great vogue in the U.S.A. But testing in Great Britain indicates that it has only limited uses as compared to, say, the much cheaper barbiturates. It is helpful in treating withdrawal states in the alcoholic. It relaxes muscle tension, and some patients with reactive tension depressions do seem to be helped by it; these patients may put on weight while on this drug.

Another group of patients which meprobamate helps are those who show mixed hysterical and obsessive phobic symptoms. These patients, when taking short-acting barbiturates, become easily addicted to them; they may also become addicted to meprobamate, and withdrawal symptoms have been reported; but so far this has not yet proved too serious a complication. Meprobamate does not help patients

*Part I of this article was published last week at p. 1031.

with pure obsessional states or deep endogenous depressions. Only 1–2 400-mg. tablets three times a day, and not more, should be prescribed where indicated.

Conclusions

Clearly sedation should not be given to patients without attempts also being made to deal with environmental and other stresses that may be a cause of the anxiety and tension. But it is a commonplace in general practice that the giving of judicious rest to the nervous system by sedation can often make problems which had temporarily seemed insuperable to a patient become quite easy to handle again. It is worth bearing in mind that the normal brain generally adjusts to its environment, and, as was very obvious during the last war, the normal brain can tolerate very bad environments indeed for very long periods of time. Likewise the last war also showed in a most convincing manner what is just as true in peacetime—namely, that once breakdown happens it is comparatively easy to abort acute neurotic reactions if only proper sedative treatment is given in time. But neurotic reactions are much less easy to treat when new abnormal patterns of behaviour and thought have been allowed to become thoroughly ingrained in brain function through the lack of adequate sedation early on in the illness. It may truly be said that a grain of sedative in time saves nine.

THE PHARMACEUTICAL HOUSE AND THE DOCTOR

BY

AUDREY Z. BAKER, B.Sc., M.R.C.S.

Medical Research Department, Vitamins Ltd., London

Recent correspondence in this and other journals has included statements that doctors are inundated by literature from pharmaceutical houses and that visits from representatives of these firms are not only unnecessary and time-consuming but contribute to the cost of drugs and the expense of the National Health Service.

The Survey

It was decided to ascertain the opinion of doctors themselves on this matter, knowing that only the few who feel strongly on the subject tend to write to the press; it was realized, however, that it would be difficult to obtain a true picture. Surveys are notoriously liable to error, whether in design, method of procedure, or interpretation, but a survey seemed to be the only practicable means.

It was considered that the effectiveness of the survey would depend on two factors: (1) the form of the questions, and (2) the way in which they were presented to the doctor.

The Questions.—(1) These must take only a very short time to answer. (2) They must be such that the answer would be unequivocal.

The Presentation.—(1) The doctor must be assured of his anonymity. (2) He must be asked but not pressed to answer.

Bearing these points in mind, a punch-card was designed with all the questions on one side, so arranged that only a tick or cross was needed in the appropriate spaces.

Knowing the almost universal distaste for questionaries arriving by post, we gave supplies of blank cards to our representatives and instructed them as follows: "Carry out an interview in the usual way, and, when you are about to leave, ask a doctor politely for his co-operation in filling in the answers to some questions which are of interest to us—pointing out that this will take only about a minute. If any doctor prefers not to do so, do not press him, but record the number of such refusals each day." The representatives were further instructed to complete the back of the card themselves but not to enter the doctor's name anywhere.

All doctors visited were to be presented with cards, and all completed cards were to be returned to us each day.

Please indicate your choice in the appropriate square

1. Do you see medical representatives?	ALMOST ALWAYS	☐	OFTEN	☐	SELDOM	☐	HARDLY EVER	☐
2. How many times per annum would you prefer them to call on you?	THREE TIMES	☐	TWICE	☐	ONCE	☐	NEVER	☐
3. Do you read advertisements for pharmaceutical preparations? ..	ALMOST ALWAYS	☐	OFTEN	☐	SELDOM	☐	HARDLY EVER	☐
4. Which journal?	B.M.J.	☐	LANCET	☐	OTHER	☐		
5. Do you prefer information on preparations?	AS ADVTS. IN JOURNALS	☐	DISCUSSED WITH REPS.	☐	SENT IN THE POST	☐		
6. Would you be willing to co-operate in any future survey of this kind?	YES	☐	BY INTERVIEW BY POST	☐	NO	☐		

Front of card.

This is an attempt to find out the views of doctors on methods used by pharmaceutical firms.

All replies are anonymous but an analysis of the results obtained will be sent on request.

For office use only	
General practice	
Consulting physician	
Consulting surgeon	
Hospital staff	
Area	

Back of card.

Classification of Responses.—Cards were appropriately punched on receipt and were filed until enough had been received. The number used in the survey represents 10% of the total number in the National Health Service.

Results

The results are shown in the Table, from which the following observations can be made:

1. Less than 3.5% of the doctors interviewed failed to reply. This figure may be misleading because it takes no count of doctors with whom the representative failed to obtain an interview; but of those who replied, more than 80% said that they almost always see medical representatives.

2. Percentage variations in the replies to certain questions were so slight even in widely separated areas that a strong presumption seems justified that the answers are a true representation of medical opinion and not due to the influence

Table Showing Area Distribution

	Scotland		N. Ireland		N. England		W. England		East and Home Counties		London		Total All Areas	
No. interviewed	569		340		867		804		651		304		3,535	
,, not replying	2		0		7		51		28		38		126	
Replies for analysis	567		340		860		753		623		266		3,409	
Question		%		%		%		%		%		%		%
1. Do you see medical representatives?													3,409	
Almost always	519	91	305	90	759	88	656	87	501	82	187	69	2,927	86
Often	44	8	35	10	88	10	84	11	113	18	71	26	435	13
Seldom	4	1			9	1	9	1	5	1	7	3	34	1
Hardly ever					4	—	4	—	4	1	1	—	13	0·4
2. How many times a year would you prefer them to call on you?													3,405	
Three times	284	50	201	59	160	19	176	23	148	24	76	28	1,045	31
Twice	243	43	131	39	550	64	436	58	367	59	133	49	1,860	55
Once	36	6	7	2	137	16	132	18	99	16	50	19	461	14
Never	4	1	1	—	10	1	5	1	6	1	6	2	39	0·9
3. Do you read advts. for pharmaceutical preparations?													3,394	
Almost always	96	17	98	29	186	22	136	18	102	16	72	27	690	21
Often	195	34	124	36	403	47	343	46	283	48	115	43	1,463	43
Seldom	210	37	92	27	192	23	187	25	158	25	57	21	896	26
Hardly ever	62	11	24	7	76	9	85	11	77	12	21	8	345	10
4. Which journal?													4,952	
B.M.J.	513	90	273	80	773	90	665	89	523	84	226	84	2,973	87
Lancet	57	10	28	8	115	13	81	11	126	20	82	30	489	14
Other*	323	57	146	43	360	42	311	42	251	40	99	37	1,490	44
5. Do you prefer information on preparations?													4,155	
As advts. in journals	122	21	51	15	300	35	175	23	164	26	111	41	923	27
Discussed with reps.	525	92	304	89	646	75	602	80	513	83	212	79	2,802	31
Sent in post	55	10	22	6	139	16	114	15	72	11	28	10	430	13
6. Would you be willing to co-operate in any future survey of this kind?														
Total replies													3,394	
Yes													3,207	94
By interview													1,344	40
By post													260	8
No													187	6
Not stated													1,603	—

More than one reply was given on some cards to questions 4 and 5. Some cards omitted replies to questions 2, 3, and 6. It is a coincidence that the numbers of omitted replies to questions 3 and 6 were the same, for a check has shown that they were not necessarily omitted from the same cards.

* Many filled in *Practitioner*.

of the interviewer; for example, in areas as far removed as Scotland and the West of England the answers to question 1 show the following sequences respectively: 91%, 8%, 1% (Scotland); 87%, 11%, 1% (West of England). Similarly, answers to question 4 indicate a *British Medical Journal* readership of between 80 and 90% throughout all areas, and answers to question 5 show that nowhere do more than 16% of doctors prefer obtaining information through the post. Such widespread lack of variation points to a greater significance where variation does occur.

3. *Examples of Area Differences in Pattern.*—In both Northern Ireland and Scotland the preference is for visits from representatives three times a year. In all areas in England the preference is for twice a year. There is a higher readership of the *Lancet* in the London area and the area including the Home Counties than elsewhere.

4. *Other Observations.*—Except in the London area, over one-third of all the doctors interviewed seldom or hardly ever read advertisements in journals. Approximately 80% prefer information from discussion with medical representatives. Only about 12% prefer information sent in the post. Classification according to the type of professions practised does not bring to light new facts, but data reveal the known link between consultant physicians and residence in the London area. Further analysis into counties and some of the larger conurbations provides numbers too small for conclusions to be drawn from them. Over 90% of the doctors interviewed expressed willingness to co-operate in a future survey. Among these five times as many preferred an interview to a postal request. Four doctors asked for copies of the survey. Reprints of this paper will be sent to them when available.

I am grateful to the medical representatives who collected the cards and to my assistant, Mrs. I. Winckler, who assembled the data.

TOOLS OF BIOLOGICAL RESEARCH

SYMPOSIUM AT GUY'S HOSPITAL

[FROM A SPECIAL CORRESPONDENT]

The Surgical Research Society held a very successful symposium on the "Tools of Biological Research" at Guy's Hospital on October 10 and 11. Mr. H. J. B. ATKINS was responsible for the arrangements. Although the different communications covered an almost bewildering range of subjects, unity was achieved because every speaker first described a technique, its physical principles and limitations, and then showed how it had contributed to knowledge. The detailed proceedings are to be published by Messrs. Blackwells Scientific Publications Ltd.

Strategy and Tactics

In an introductory address, Sir CYRIL HINSHELWOOD, President of the Royal Society, said that the most economical campaign in research usually employed the newest methods. But it was successful only if it had a well-conceived master-plan. Any individual worker might be a specialist in his technical methods, but he should not be so in his thinking and knowledge; the more he was called upon to supervise the work of others, the more he must know what techniques were available and so avoid the tendency common to most of us, to continue to fight the last war. To neglect modern techniques was to be amateurish. They were highly complex and often demanded team-work, but collective action to be its most beneficial must provide opportunities without imposing restrictions.

Dr. PETER ARMITAGE said the original expansion of statistical technique owed much to Carl Pearson, but it was after

the work of Sir Ronald Fisher, which was initiated for agricultural experimentation from 1920 onwards, that the use of statistics in the laboratory and in medicine became established. Biological trials rarely gave the same answer twice, only a broad repeatability, and statistical techniques were especially applicable to such results whether the units were patients or agricultural plots. Dr. Armitage illustrated, with clinical examples, Fisher's three main principles of : (1) randomization, (2) replication, and (3) local control of variability. Within a controlled trial "randomization" was no haphazard allocation of subjects to an experimental or a control group, but must be a real chance mechanism whereby the probability of those doing well in the groups, irrespective of treatment, could be calculated. "Replication" was widely practised and was always useful as a basis for wider generalization from results. If the effect tested produced a large change, few observations would suffice ; but often that was not so, and the question of how many observations to make was always arising. The statistician would ask the research worker, How variable is your material and what is the smallest difference you don't want to miss ? Then the answer could be given. But this information was rarely forthcoming ; often it had itself to be found by careful design and experiment. The third principle of "local control of variability" led to the efficient design of experiments, and Dr. Armitage reviewed the use of the Latin square and the technique of factorial experimentation. He finished by showing how useful sequential analysis could be in clinical work where the maximum number of observations was restricted, as it allowed the trial to be stopped earlier than with other methods if a satisfactory difference emerged.

Flame Photometry

In the first communication on a physical instrument Professor R. H. S. THOMPSON and Dr. R. W. R. BAKER were dealing with a generally familiar technique. Dr. Baker therefore concentrated on the detailed construction of each component of the flame photometer: the flame to be hot enough and constant was best fed from gas compressed in cylinders, the spray needed to be fine enough so as not to cause cooling of the flame, the characteristics of the light filter had to be studied, and finally there was the choice of photo-cell, each type with certain merits and disadvantages. The introduction of the internal lithium standard had been an advance, because any fluctuation in the flame was now reflected in the standard as well as in the analyser. With the new instruments not only could sodium and potassium concentrations be quickly and accurately measured in biological fluids, but calcium (which had hitherto presented many difficulties with this method) could be measured within about 2% of the theoretical amount, and the results were better than by chemical titration.

Electromanometry

Dr. J. P. SHILLINGFORD pointed out how recent was the evolution of electromanometry compared with other methods of pressure measurement in biology. In every device for this purpose diaphragm movement was converted into change of electrical potential, and all had the fundamental requirements (which were not independent) of sensitivity, low volume displacement to give adequate frequency response, stability, linearity of response, and ease of handling and sterilization. He then discussed the working principles and merits of each of the different types of instrument available: the capacitance manometer, the strain-gauge, the inductance manometer, the transducer valve, and the photoelectric manometer. A new advance was the use of an inductance manometer so small as to fit into the end of a cardiac catheter. This got over the errors inherent in using a long tube between the site of pressure variation and recording, but the disadvantage was the cost of about £80 for a catheter containing the minute manometer, which could be used only about a dozen times. He finished by showing the difficulties in measuring pressure gradients across heart valves.

Tissue Culture

Modern technique has two main branches: cell culture and organ culture. Dr. HONOR FELL, F.R.S., said that for detailed cytological studies the original hanging-drop method of cell culture, using a medium containing embryo extract while maintaining strict asepsis, was still valuable. But it was most laborious for long-term studies, and for this purpose had been replaced by the flask or roller-tube techniques, which she described. There remained two difficulties with cell culture: the production of a stable culture of pure cells, and the production of synthetic media to replace those containing plasma and embryo extract. Since the tissue fragments used to start cell cultures contained many cells, many cell-types proliferated ; and, even if one type finally became predominant, it was impossible to say that subcultures from it were "pure cultures," for different cells might appear alike in culture. But in 1948 the first "clones" (populations derived from a single cell) were produced from mouse fibroblasts, and recently clones of human epidermal cells had been grown. Such really pure cultures might exhibit cell transformations, and some of these had proved to be malignant. This *in vitro* production of cancer was of great interest, as its causes could be investigated. However, the complexity of substituting artificial media in the analysis of cultured factors was enormous—even with media containing upwards of 60 different amino-acids, vitamins, and hormones cells would degenerate in a few days, although readily revivable with tissue extract. Cell culture had also proved its worth in virology ; without it, there was no way of growing viruses *in vitro*.

Organ culture, continued Dr. Fell, was laborious. The explant must be compact, as no blood circulated and food and waste products had to pass between the medium and the explant's surface. Profuse growth and cell migration disrupted the tissue architecture, and internal necrosis occurred ; once an optimum size had been achieved, cell growth must be made to balance cell degeneration, as in the body. A rayon-cloth base had proved useful in growing flat tissues. Organ culture was better than cell culture for the study of the effects of vitamins, carcinogens, etc., though the *in vitro* tissue response, while qualitatively like that *in vivo*, quantitatively was often greater because of the poorer excretion. Negative results had to be interpreted with great caution. Dr. Fell finished by giving a fascinating account of the action of vitamin A as an illustration of the potentialities of this technique. *In vivo* it was well known that its lack caused keratinization. *In vitro* the opposite effect could be observed ; an excess caused the disappearance of keratin and the conversion of skin into a mucus-secreting epithelium containing goblet cells.

Tissue Transplantation

This topic followed naturally after tissue culture *in vitro*. Dr. L. BRENT confined his remarks to the technique and uses of homografting (where tissue from one animal is transplanted to another of the same species), which, though complex, present fewer problems in the analysis of a host's reaction to foreign tissue than the use of heterografts, where there is the added factor of species difference. All homografts (save in exceptional cases, such as the cornea which was not vascularized or in homografts between identical twins) were destroyed, and the technique of transplantation could be used to investigate (1) why homografts were unacceptable, (2) how their destruction was accomplished, and (3) how to prevent the host's response. Skin was the most useful material for study ; it was easily transplanted, could be directly observed, and was readily available for biopsy. Animals could be immunized against the effects of homografts, and Dr. Brent showed examples of homografts behaving like autografts in animals which had been immunized when young. But if during immunization too many cells were injected into the young animals they failed to

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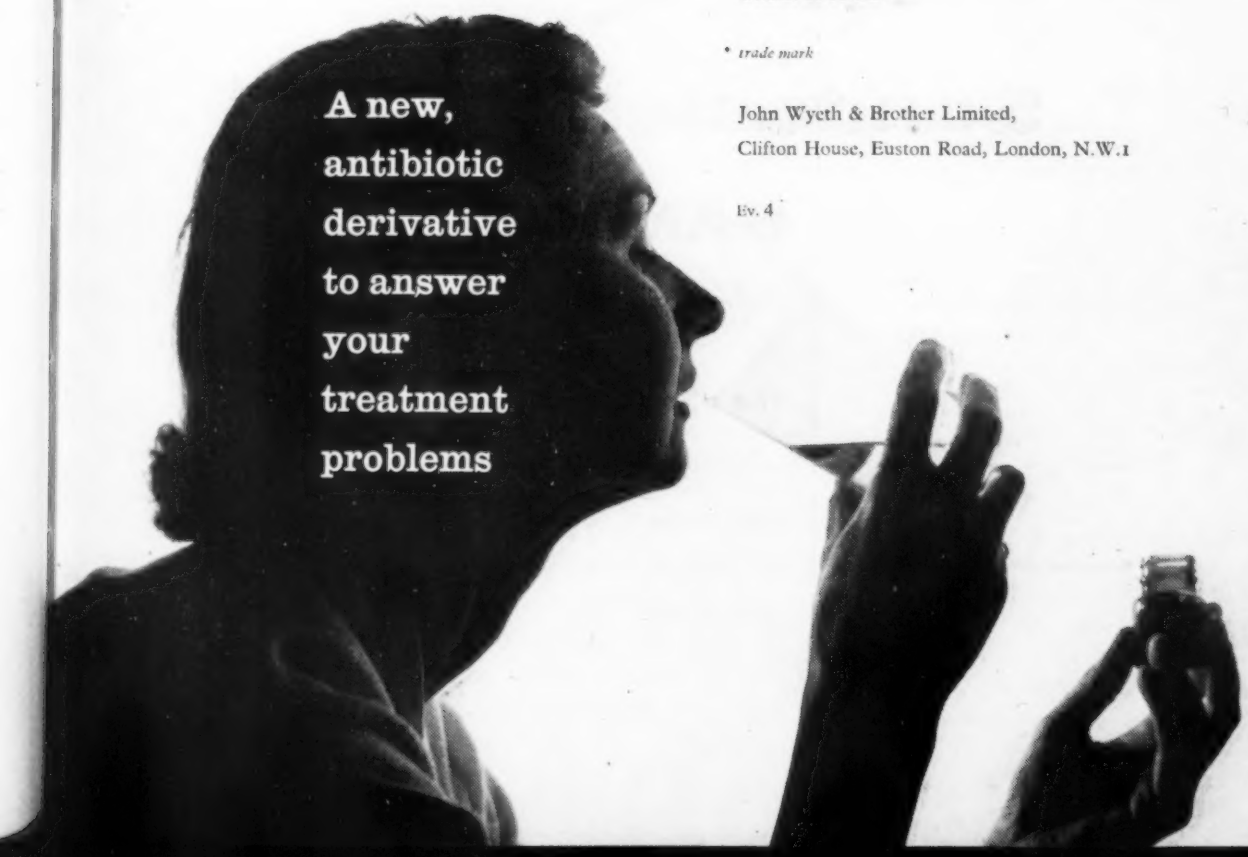

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grow normally, developing a kind of "runt" disease. Tolerant animals could still exhibit intolerance to foreign tissue if injected as adults with normal lymphoid cells. The mechanism of intolerance appears to lie in cells rather than in the usual circulating antibodies. In response to a number of questions, Dr. Brent described the use of porous chambers in which tissue could be protected from cellular antagonists within the body of a host animal, and discussed the possible use of this technique for the implantation of ductless glands in man. Finally, he answered a question on the effects of massive *x*-irradiation in preventing reaction to heterografts by supposing it acted by destroying all the host's lymphoid tissue; such irradiated animals could be saved from death by transfusion of heterologous as well as homologous blood and lymphatic tissue, but unfortunately they then react to the repopulating cells and die of a type of "runt" disease.

Electrophoresis

In a lively presentation, Professor N. H. MARTIN described a technique familiar to most of his audience. Using the analogy of sand particles being dropped into champagne and producing a minute electric current as they fall, he described the converse—moving particles by applying an electric current—in terms of moving a block of protein within a tube of a suitable buffer, since electrophoresis is usually applied to protein analysis in medicine. The different components of the protein block move in the electric field at different rates, and from measurement of the rate of change of refractive index along the leading and trailing edges it is possible to represent the components as different peaks, those from one edge giving a record which is usually a near mirror-image of the other. The classical equipment is expensive and costly, but the introduction of paper electrophoresis has made the whole technique much simpler. He reviewed some of the results from this useful tool.

Electron Microscopy

The invention of the ordinary compound microscope increased our visual range about a thousandfold, and the electron microscope has increased our field of view as much again. Dr. DAVID ROBERTON said the foundations of electron microscopy dated from 1924, when it was realized that a moving electron beam had an associated wavelength and could be focused by electrostatic or magnetic "lenses." The need for the object to be exceedingly thin, and for it to be able to withstand a temperature of 80° C. and the high vacuum in the machine, limited the role of electron microscopy in biological work, precluding the observation of living material and making the techniques of preparing specimens difficult. But microtomes which reproducibly advanced by as little as 100 Å between cuts were now available (driven either by screw threads or the thermal expansion of metal rods), and the cutting of such thin sections had been made practicable by the use of small disposable knives made of freshly broken glass. "Araldite" plastic (well known to laboratory workers for its adhesive and coating properties) had proved itself to be a satisfactory embedding material. Now that a reasonably satisfactory technique for preparing specimens was available, electron microscopy had made possible some very exciting advances in our understanding of cell structure.

They started with the observation of a layered appearance of a section of myelin from a nerve sheath; the layering proved to be caused by nerve axons being buried "within" Schwann cells, the walls of the latter being deeply indented by the axon to form a "mesaxon" connecting with the outside. Spiral layering of these mesaxons produced myelin. From a comparison of *x*-ray diffraction patterns with the layers seen in the walls of animal cells under the electron microscope it seemed likely that all cells had a similar type of molecular structure in their walls, composed of a basic bimolecular leaf of lipids with a polar surface free for the attachment of protein and other molecules.

Image-intensification

The strain of having to use a foreign language, rather than his native Dutch, in no way marred the polished description of image-intensification by Dr. B. COMBEE. In spite of the great advances in radiological technique since Roentgen, there had been no new method of detecting the rays, and the original methods of direct inspection of the fluorescent screen or of photography were still in use. With the fluorescent screen the radiation dose to the patient had to be large to produce even a low light intensity on the screen. In the intensifier the *x*-ray beam from the patient hit a fluorescent screen in a low-pressure tube, whence the emergent light quanta immediately impinged on a photocathode. This cathode emitted electrons which could be accelerated to an anode acting as a second screen, where visible light was again produced. The small but brilliant image at the second screen was then magnified by an optical lens system. The intensifier could be used in a number of ways—for example, to lower the radiation to the patient during fluoroscopy, to produce a high illumination of the screen so that it could be viewed in a lighted room such as an operating theatre, or to enable ciné films to be taken of the image. Dr. Combee showed a film of cholangiography taken during surgical operation.

Phase-contrast and Interference Microscopy

Dr. R. BARER not only explained the principles of these theoretically complicated techniques, but succeeded in showing how by their use it was possible to weigh an individual cell under the microscope. Simple calculation from the approximate diameter and density of, say, a staphylococcus, showed that its weight is about 5,000 times less than what can be measured with the best analytical balance. It was not possible to weigh under the microscope in the ordinary sense, but quantities related to weight could be measured. Refractive index, for instance, was a measure of the amount of matter present; it depended on the number of atoms and their compactness, and was proportional to the concentration of solutions. Dr. Barer mentioned some recent advances with the technique. In one, the haemoglobinometry of a single red cell had been achieved and different populations of cells had been found in different disease states; in another, unique to the technique, the changes in concentrations of solids in the lymphocytes of *x*-irradiated mice had demonstrated the latent liberation of a toxin during the recovery phase; and in a third the mycologists had been provided with a means of distinguishing the plus and minus strains of fungi during their reproduction.

Mass Spectrometry

This technique, which has allowed well-known and fundamental advances in physics, has recently been developed for clinical use in respiratory studies to provide rapid, simultaneous, automatic analysis of up to four constituents in very small samples of a gas mixture. Dr. P. HUGH-JONES described how this method of gas analysis enabled the rapid changes in gas concentration during breathing to be followed, not only at the lips but for the first time within the different lobes and segments of lung. The principle of the technique was that molecules of each individual gas are separated according to their mass. The molecules were first electrically charged by ionization, accelerated by an electric field into a narrow beam, and then passed through a magnetic field which deflected their path by an amount depending on the accelerating voltage and their charge and mass: the lighter the molecules the greater the magnetic deflection. After describing the special spectrometer for respiratory work which Dr. K. T. Fowler had designed,* Dr. Hugh-Jones indicated its potentially wide field of usefulness in research and clinical medicine. He confined himself to results obtainable only with this technique. Sampling at the lips during

(Continued at foot of next page)

*See Fowler, K. T., and Hugh-Jones, P., *Brit. med. J.*, 1957, **1**, 1205.

To-day's Drugs

In this column we publish from time to time authoritative notes on a selection of drugs in current use.

Predsol and Predsol-N (Glaxo Laboratories Ltd.).—Ointments and lotions containing 0.25 or 0.5% prednisolone disodium phosphate, with the addition in predsol-N of neomycin.

Deltacortril DA (Pfizer Ltd.).—Prednisolone diethylaminoacetate hydrochloride 0.25% in an ointment with a greasy base.

Precortisyl (Roussel Laboratories Ltd.).—Prednisolone in a 0.5% cream or 0.25% lotion.

The value of hydrocortisone and of combinations of hydrocortisone with neomycin in the treatment of various skin diseases has been well established by clinical use in the course of the last two years or so. It is natural that prednisolone should be put to the same purpose in preparations such as these. They seem to be of a suitable strength, and their clinical effectiveness is very difficult to distinguish from the corresponding hydrocortisone applications. There will be little to choose between these preparations and those containing hydrocortisone, but individual patients may do better with one or the other. As with hydrocortisone, systemic absorption is minimal, and even when large areas are being treated the mildest systemic effects are most unlikely.

N.H.S. basic price: predsol lotion 0.1%, 20 ml., 5s.; 0.25%, 20 ml., 9s.; predsol ointment 0.25%, 5 g., 3s.; 0.5%, 5 g., 5s. 6d.; predsol-N ointment 0.25%, 5 g., 3s. 9d.; 0.5%, 5 g., 5s. 7½d.; deltacortril DA ointment, 5 g., 4s. 6d.; precortisyl cream, 5 g., 5s.; precortisyl lotion, 20 ml., 9s.

Aturbane (Ciba Laboratories Ltd.).—This product has, under the title Ciba 10870, been tested as a palliative measure in cases of Parkinsonism, whether idiopathic or post-encephalitic. It comprises an α-phenyl-α-(diethylaminoethyl) glutarimide hydrochloride, and is parasympatholytic in action. Pharmacologically it is capable of relieving spasm induced by acetylcholine. Clinically it has been found helpful in relieving the excessive salivation and the muscular rigidity of Parkinsonism. Any effect upon tremor and upon oculogyric crises is not usually obvious. Side-effects that have been observed include mental confusion, euphoria, dryness of the mouth, nausea, and vomiting, but all apparently slight in degree with ordinary therapeutic dosages. Glaucoma contraindicates the use of this drug. The drug is a white crystalline powder, soluble in water, dispensed in 5-mg. tablets. The suggested dosage is 10 to 20 mg. daily, though in exceptional cases as much as 50 mg. a day may be given.

N.H.S. basic price: 100 tabs., 17s. 4d.

(*Continued from previous page*)

a single expiration provided a practicable routine means of measuring the balance between gas and blood distribution in the lungs, so vital to the understanding of the functional pathology of many forms of respiratory disease; while sampling from different lobes or segments of the bronchial tree during diagnostic bronchoscopy had opened an entirely new field. Animal experiments showed that specific changes in gas-concentration patterns were associated with reduction of the air-flow or blood-flow within a lobe. It now seemed likely that the ventilation, blood-flow, and some mechanical properties of diseased lobes or segments of the human lung could be measured before surgery. The technique had also enabled the patterns of gas-flow within the bronchial tree to be measured, and a number of future applications in medicine, surgery, and paediatrics were envisaged.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Addiction to Unrestricted Drugs

SIR,—I think Drs. C. P. Seager and A. R. Foster (*Journal*, October 18, p. 950) have not considered the problem of carbromal addiction adequately. According to them an addictive drug should show one or more of the following properties—viz., craving, tolerance, dependence. One other characteristic could be added—i.e., the recipient should either derive pleasure or prevent distress. The morphine (or heroin) addict takes the drugs either for euphoria or to prevent withdrawal symptoms. Whilst under the influence of the drug he is normal physically and mentally. The three cases of carbromal overdosage described by Dr. Seager resulted in most disagreeable symptoms. No addict would have put up with such discomfort for one moment, neither would a normal person. The authors admit that these cases were psychopathic. They certainly exhibited masochism to a marked degree. It is because the normal person is neither psychopathic nor masochistic that such cases, due to carbromal, are almost non-existent. I cannot, therefore, agree with the authors' conclusion that the open chain ureides should be restricted. The mild insomniac should be able to obtain his sedative without hindrance; the presence of a few psychopaths in the community is insufficient warrant for alteration of the schedules.—I am, etc.,

Melbourne. F. H. SHAW.

SIR,—In their article on addiction to unrestricted drugs (*Journal*, October 18, p. 950) Drs. C. P. Seager and A. R. Foster draw attention to the risks of habituation and addiction attending the unrestricted sale of certain non-barbiturate drugs. All the drugs they mentioned have been noted in our experience, too, to give occasionally rise to habitual abuse in large, often increasing, doses by unstable people, chiefly alcoholics of a hysterical, immature, and inadequate, or psychopathic, personality-type, who in the past often had also taken to excess barbiturates and amphetamines. Most frequent was the misuse of "persomnia" (a finding confirmed by several doctors in this country with experience in the treatment of alcoholics), and there were occasional cases of habitual excess of carbromal itself and "relaxa-tabs" (another carbromal-bromvaletone preparation), chlorodyne, and the stimulant "preludin." One alcoholic took large, increasing doses of meprobamate. Two cases were seen of habituation to glutethimide, one to methyprylone (two non-barbiturate hypnotics which otherwise were found to be safe and effective in several hundreds of patients). Sometimes these people drank to excess simultaneously with taking excessive doses of the drugs, but in general the picture was similar: confusion, incoordination, and slight slurring of speech. There seemed to be a great desire to take large doses of the drugs in increasing amounts, but there was no real evidence of "compulsive craving" or of physical dependency in the form of a withdrawal syndrome.

Warnings against the risk of habit formation arising out of the indiscriminate use of such drugs have of course also been raised in other countries. Thus an American study[1] reports 72 cases of habituation and one of addiction following the use of tranquillizing drugs among 8,200 patients suffering from an anxiety state. In the case of meprobamate several observers noted the occurrence of withdrawal symptoms when the drug was discontinued.[2,3] The W.H.O. Expert Committee on Addiction-producing Drugs states that "cases of misuse (of tranquillizing drugs) are being reported with increasing frequency,"[4] and believes that tranquillizers "must be classed as potentially habit-forming."[5] German authorities have reported cases of habituation and addiction to meprobamate,[6] 1-ethinyl-cyclohexyl-carbamate (a non-barbiturate hypnotic),[6,7] and preludin.[6,8] Swiss doctors

describe the abuse and addiction to "so-called harmless" analgesics (sometimes containing phenacetin)—not affected by the "*Betäubungsmittelgesetz*"—leading on sudden withdrawal to severe abstinence symptoms, with epileptiform fits, deliria, and hallucinoses.[9 10]

Apparently among certain unstable, predisposed personalities any drug producing a feeling of improved well-being[1]—perhaps by helping them "to get rid of something" (such as tension and anxiety) or "to get hold of something" (euphoria)—can lead to abuse and, at least, habituation. It therefore seems regrettable that again and again new drugs (as, e.g., a recently introduced non-barbiturate hypnotic) are described and advertised as not giving rise to habituation or addiction.—I am, etc.,

Southall, Middlesex. M. M. GLATT.

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5 Ibid., 1957, **116**, pp. 10, 13.
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8 Rommeney, G., *Die sozialmedizinische Bedeutung der Arzneimittelsuchten*, *Hamm*, 1957, p. 20.
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10 Kielholz, P., *Schweiz. med. Wschr.*, 1957, **87**, 1131.

Oesophageal Stricture

SIR,—The papers by Mr. J. A. W. Bingham (*Journal*, October 4, p. 817) and Mr. K. C. McKeown (*Journal*, October 4, p. 819) draw attention to oesophageal stricture as a complication to the surgical treatment of peptic ulceration of the stomach and duodenum, and the authors put forward a number of possible causes. A study of their case records shows that 5 of the 6 patients had hiatus hernia with a short oesophagus to a marked degree, and that, although this condition certainly existed prior to operation, it was not recognized clinically or radiologically. The sixth patient (McKeown's Case 2) had the symptoms of a reflux oesophagitis, and the operative findings were suggestive of gastric mucosa lining the lower oesophagus. The type of hernia found, with shortening of the oesophagus, is one very commonly associated with oesophagitis, and it thus appears that all these patients had oesophagitis prior to their operative treatment for peptic ulceration of the stomach or duodenum.

The moral is that the symptoms of hiatus hernia and oesophagitis are overshadowed by the more severe symptoms of gastric or duodenal ulceration, until these latter symptoms are relieved by gastrectomy, whereupon they become noticeable. In many cases the removal of acid or pepsin secretion may well lead to the oesophagitis subsiding and giving no further trouble, but in some cases the oesophagitis will have been of such severity that it will heal by fibrosis and stricture formation, leading to more severe symptoms such as those described by the authors in their papers.—I am, etc.,

Harefield, Middlesex. K. S. MULLARD.

Hiatal Herniorrhaphy

SIR,—In your issue of September 20 (p. 728) Mr. J. Borrie describes the right-sided approach for hiatal herniorrhaphy. He says "to date no record has been encountered of a right-sided approach for repairing such hernias." I repaired a hiatus hernia in Lewisham Hospital with Mr. J. Jemson on April 11, 1951, using the right-sided thoracic approach. I did this under the mistaken impression that Russell Brock, who to me represents the law and the prophets in all things surgical, recommended it. I found it very difficult and very unsatisfactory, and I vowed never to try it again and never have.

I waited to comment till I had traced the patient. I find that, after being free from symptoms for eighteen months, he returned to Guy's with dysphagia, and *x*-ray showed that his hernia had recurred. Robert Brain did a re-repair through the left chest in September, 1953, and the patient has since remained well. This 100% recurrence in a solitary venture compared with more than twenty repairs done through the left chest at the Royal Masonic Hospital, Guy's, and Machynlleth, none of which has as yet recurred, so far as I have been able to discover.—I am, etc.,

London, W.1. HENEAGE OGILVIE.

Mass Casualties from Nuclear War

SIR,—The paper[1] criticized by Dr. M. C. Berenbaum (*Journal*, September 27, p. 800) is very far from preaching complacency in face of nuclear attack: it is equally far from proclaiming a policy of inactivity and despair. He has not made himself familiar with the premises of the argument he opposes. Briefly, they are that in a mass casualty situation there can never be enough doctors or nurses on site to attend to all the injured: that, in consequence, non-professional men and women must be trained to accept responsibilities that up to now have rested entirely on doctors and nurses. Also that, since casualty sorting is the key to effective management of large numbers of casualties, a filter organization must be created, to prevent the hospitals further back from being overwhelmed either by the lightly injured or by those the hospitals will be unable to help.

We set out to estimate the greatest number of casualties which a given group of medical personnel forming a filter unit could effectively sort and treat in 24 hours. It was thought that this number might be in the region of 6,000. Experiments and time-and-motion studies have been made, to estimate whether a filter unit of the size described could deal with this task. Obviously there is a theoretical element to such tests, but the conclusion reached by the great majority of those to whom the problem has been demonstrated is that suitably trained personnel should be able to do so.

The paper in question, with the hand-out which accompanied it, gives a staffing list of the various departments of a filter unit and also shows among other definitions that the urgent surgery envisaged is limited to simple procedures such as control of bleeding, dealing with rapidly correctable respiratory defects, completion of incomplete amputations, and splinting of compound fractures of major bones. Many such cases will not need a doctor's attention but can be dealt with by others. From these documents, which I now quote because they had a limited circulation, it can be seen that in fact each of 1,200 patients to pass through the immediate treatment (urgent surgery) department would indeed have 9.6 minutes under active team treatment, or a total of 28.2 minutes of nurses' or nursing auxiliaries' time plus 3.6 minutes "doctor's time." This would be achieved by a staff of three doctors and eight teams each consisting of three nurses or nursing orderlies.

Effective casualty sorting, the key function of a filter unit, is a problem that can be tackled, but not by one surgeon as Dr. Berenbaum assumes. To sort 3,600 cases in 24 hours would be the work of two surgeons plus at least two other doctors, working as a team with 12 nursing orderlies to help them. The plan would be for the two doctors to decide upon the disposal of the more obvious cases, and call in the surgeons only when in doubt. The surgeons and doctors have 1.6 minutes to examine the cases referred to them—and by this time the injured will have had clothing removed and their injuries exposed. Experienced surgeons who have witnessed trials have said that casualty sorting of the kind needed in a situation such as this can be performed within this time.

I sincerely trust that readers of this correspondence will feel able, conscientiously, to join in a plan which, in our opinion, can help the victims if we should ever be faced with this kind of disaster.—I am, etc.,

Farnborough, Hants. T. M. R. AHERN.

REFERENCE

1 Ahern, T. M. R., *Proc. roy. Soc. Med.*, 1957, **50**, 968.

SIR,—Many of us interested in the medical aspects of civil defence may possibly agree that Dr. G. D. Kersley's paper (*Journal*, August 9, p. 379) may not produce the effect he desires, but the effects will be much more useful than the suggestions of Dr. M. C. Berenbaum in his letter (*Journal*, September 27, p. 800). Some of the most severe critics of the present civil defence arrangements and of their presentation to the community are themselves in civil

defence. It is only by propaganda directed at the Home Office and by energetic local action that the present inadequacies can be met, but we must never allow the statesmen to have their heads as suggested in the last paragraph of Dr. Berenbaum's letter. Even if they take responsibility for it, the medical profession will still be left to clear up the mess the politicians have created. We must tell the public the truth now and induce the Home Office to do the same. After a fairly extensive association with all workers in civil defence, I am convinced that there is not one who has any illusions about the appalling effects of nuclear warfare.

Dr Berenbaum maintains that the medical services will be disrupted if a scheme on the scale suggested by Colonel Ahern is put into action. If the country is to survive at all this scheme will be the minimum we require. Other medical services, except those of the most urgent and vital character, will have to cease even before the shooting starts. This disruption will be but one part of the total survival plan which will have to be put into operation. If we are to face annihilation and to save anything from it, every man, woman, and child and every possible activity in which they engage will have to be subordinated to this provision. Even though millions are killed and much of this country and Western Europe are destroyed, we, who believe in ourselves, must have faith that our essential values are worth saving and that this saving can be effected.

In the past the Home Office were not planning on a large enough scale. There are signs now that they are getting away from the last war mentality, and this new approach is the result of the work of knowledgeable and imaginative members of the armed Services and civil defence organizations. There are plenty of memorials in the Health Service already to the work of politicians. A vital matter like this must not be left to their unaided efforts. The medical profession has taken too little interest in civil defence, but we must now play our proper part, and make our voices heard. We cannot avoid taking responsibility for the medical services in the defence of the nation.

—I am, etc.,

Shrewsbury. E. N. OWEN.

Treatment of Asthma

SIR,—The article on the drug treatment of asthma by Dr. R. S. Bruce Pearson (*Journal*, October 11, p. 905) was both welcome and timely. It deals comprehensively and lucidly with a clinical problem which is becoming increasingly difficult in general practice, owing to the many diverse preparations which are now available, each understandably but none the less confusingly extolled by its manufacturer. May I, however, be permitted to offer some comments which arise from experience in a fairly typical general practice? The treatment of acute cases is not easy outside hospital, and I am chary of employing relatively large doses of corticosteroids on patients whom I cannot keep under continuous surveillance; in the few cases where I have tried it, I have found that corticotrophin has secured better results than the corticosteroids. Indispensable as these drugs now are in status asthmaticus, prophylatic measures outside hospital cannot usually include them, and in my view intravenous aminophylline remains the general practitioner's best standby in acute adult cases.

In less serious cases, and especially in early cases, I would suggest that sedatives can play an even more important part than Dr. Bruce Pearson suggests. I submit that all asthmatics are suffering from anxiety, and that the anxiety may be a primary cause of the asthma. In any event, anxiety predisposes to attacks, and the attacks induce more anxiety; this vicious circle can sometimes be broken by the use of suitable sedatives alone, or preferably in conjunction with antispasmodics to reduce the frequency and severity of attacks. I thus entirely concur with Dr. Bruce Pearson that a combination of sympathomimetic and xanthine substances with a sedative is most suitable in these cases, but disagree with his advocacy of keratin coating to delay absorption for prevention of nocturnal attacks.

In my experience the resin-ephedrine complex which he dismisses earlier is the most effective method of securing both sustained action for prophylaxis of day or night attacks and reduction of the side-effects of ephedrine. This preparation (I believe "asmapax" is the only one of this kind on the market) contains theophylline and sedatives as well as the resin-ephedrine complex, and thus answers both Dr. Bruce Pearson's prescription and his comment on the high price; it is difficult to compare the cost of a medicament used 12-hourly, and combining several drugs, with the several components used at shorter intervals. Upon investigation I find that asmapax treatment costs the N.H.S. an average of 2s. 4d. weekly, surely a modest sum when compared either with the cost of corticosteroids or with the saving in suffering, working hours, and night visits which I find can be effected with this preparation.—I am, etc.,

London, N.W.2. H. MARGULIES.

SIR,—As a psychiatrist treating a small but steady flow of asthmatic children and adults I wish to thank Dr. R. S. Bruce Pearson for his admirable article on the drug treatment of asthma (*Journal*, October 11, p. 905). While undoubtedly a large number of these patients have to receive palliative treatment only, and the best one can hope for is to make their lives a little more tolerable to them than it was before, there is no doubt at all that it is possible to cure a few of those that have been resistant to the orthodox management or derived only partial benefit, by the simple means of hypnosis and, especially, autohypnosis.[1]

This is not a panacea, but is, with the necessary persistence, learnable; it is not time-consuming, and has few if any absolute contraindications. Apart from the important fact that it seems to help when nothing else does in the case of some patients, many have undoubtedly the capacity for profiting to some extent; it has especially often been remarked to me that "hangover" from drugs and other side-effects are completely absent. This particular technique can be easily acquired and has been used widely in Germany. There are literally dozens if not hundreds of publications in the German language on the matter.—I am, etc.,

Derby. D. J. SALFIELD.

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[1] Salfield, D. J., *Brit. J. med. Hypnot.*, 1957-8, 9, 2.

Malaria and Anaemia in Infancy

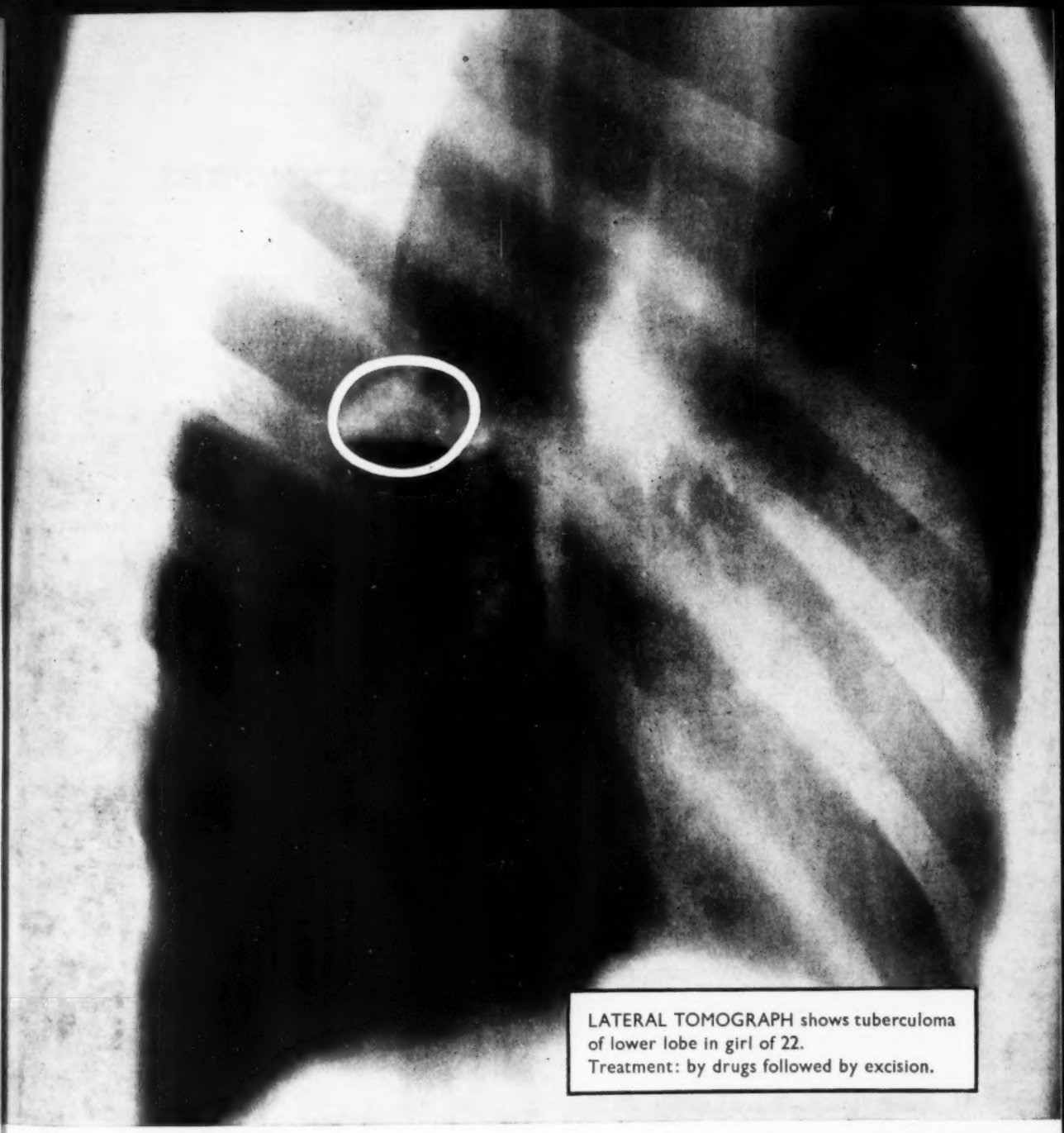
SIR,—Drs. R. G. Hendrickse and M. A. R. King (*Journal*, September 13, p. 662) have made an important contribution to the practice of paediatrics in West Africa by showing the relationship between malaria and the anaemia that is so frequent in infants here. An early verbal report of their findings had led us in this hospital to use routine suppressives on all Welfare infants. There are about 900 Welfare attendances at the hospital each week, and anaemia amongst these infants was at one time quite common. Over the last year it has been our practice to give a monthly tablet of pyrimethamine. This costs the hospital only 1.1d. per tablet. Since introducing this measure severe anaemia has become unknown amongst these children, and palpable spleens are uncommon.

Drs. Hendrickse and King offer no explanation for the frequency of negative blood-films. I should like to suggest that this may be due to small doses of quinine. The local mothers in this area are familiar with patent medicines containing quinine, and it is my experience that they may visit a local medicine stall for a dose of this before bringing their child to hospital. This small dose may temporarily clear the blood of parasites.—I am, etc.,

Wesley Guild Hospital, Ilesha, Nigeria. D. C. MORLEY.

Congenital Deaf-mutism

SIR,—Dr. L. Fisch (*Journal*, September 13, p. 692) finds it difficult to accept the evidence set out in my article (*Journal*, July 26, p. 201) on congenital deaf-mutism and criticizes the results of audiometry. I realized only too well the pitfalls associated with this method of examination, but, so far, there is no objective vibration. Awkward and



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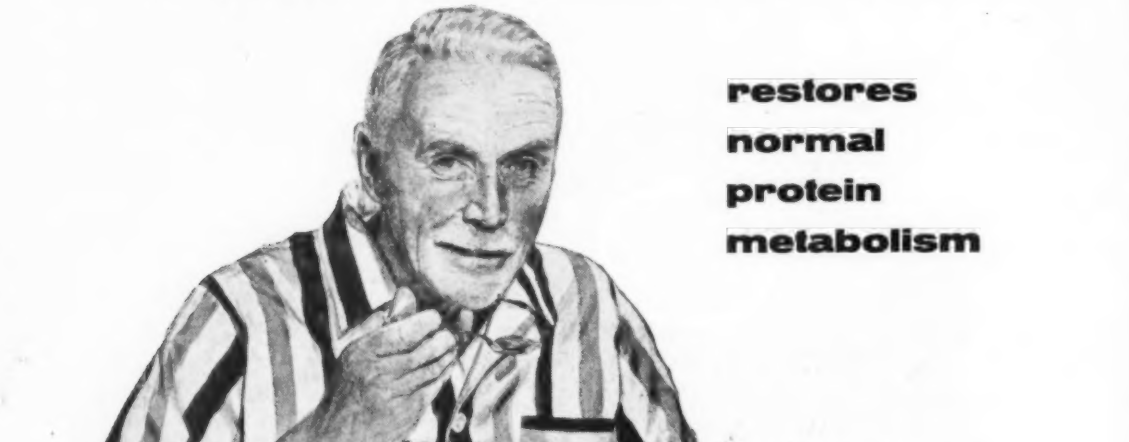

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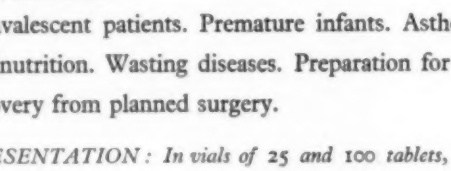

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frustrating though it be, we still depend entirely on what the patient tells us.

For record purposes the audiometer used is a Peters fitted with its standard oscillator and providing in the cases noted an interrupted signal. The children mentioned in the article had experienced the sensations of hearing by earphones and therefore had a basis from which to work. With the oscillator applied to the mastoid region by an assistant, the child was repeatedly asked to differentiate between hearing and feeling, and, at the frequencies and intensities indicated, the answers were definite. In every case the signals were gradually increased from the minimal intensity up to the point of hearing.

Concerning the identical appearances of the audiograms noted by Dr. Fisch, it should be pointed out that since the original tests in May, 1957, repeat examinations have shown distinct variations in the curves although there remains in each the general pattern of bone conduction readings at lower intensities than air conduction.

The fact that the inner ear of the congenital deaf-mute is defective on histological examination may suggest that the initial lesion was in the cochlea, but tacit acceptance of this ignores (*a*) the association of deaf-mutism with congenital defects of the first visceral arch, (*b*) the complete absence of any recorded instance of other labyrinthine disorders in the deaf-mute child, and (*c*) the normal radiological appearance of the bony cochlea in deaf-mutism.

Mr. Bauer, who also finds my arguments unconvincing (*Journal*, October 4, p. 588), quotes the condition of bilateral congenital atresia of the auditory meatus with malformation of the incus to show that excellent inner-ear function may exist with an abnormality of the middle ear, but this does not mean that all middle-ear anomalies will allow of excellent cochlear function. His suggestion that the surgeon should examine the middle ear in the congenital deaf-mute through the operating microscope is an excellent one, and, so far as I am aware, has not yet been done. Undoubtedly it is the most direct method of proving or disproving my theory of the cause of congenital deaf-mutism, and I look forward to learning the results of such an investigation.—I am, etc.,

Aberdeen. JOHN MCKENZIE.

Imbecile Children

SIR,—Dr. C. Guy Millman (*Journal*, October 4, p. 859) suggests that mentally defective children may die just as readily at home as in an institution, and that the high death rate which we reported in the post-admission period may therefore not be significant. He adds that one would not expect skilled nursing and medical attention to hasten the death of the children.

We do know that children on our waiting-list sometimes die at home. We wished, however, to draw attention to the very high death rate in the post-admission period. The figures which we reported provide an internal control, since they show that the death rate is related to the admission of the patient to hospital. If the children die merely because they are delicate, then there is no special reason why the deaths should be concentrated in the post-admission period. There is no question of the children being acutely ill on admission to hospital. They have been on our waiting-list for up to three years, usually at least one year, and we do not admit acutely ill children—they are referred to a paediatric department.

The problem of post-admission deaths merits further study. It is well known that there is a certain risk in admitting young children to hospital. In this respect mentally defective children seem to react like much younger children. We think that the excess of deaths can be partially explained on the following grounds:

(1) *Infection.*—Very backward children have often been rather isolated prior to admission and have not mixed with other children very much. On entering a large overcrowded ward they are exposed to a very considerable battery of mixed infection, much of which is new to them.

(2) *Stasis.*—At home most of these children are picked up, nursed, and moved a good deal by their mothers and others. With the very limited nursing staff available this is not possible in hospital. This is particularly important in cripples. Static pneumonia associated with inefficient cough reflex and repeated inhalation of small quantities of food is the common cause of death.

(3) *Change of routine and fretting.*—Despite their low intelligence, our children have become accustomed at home to a certain diet, method of feeding, maternal attention, and so forth. Hospital admission means a sudden disturbance of this routine, with much reduced attention. Part of the loss of weight and other changes which so often follow admission may be attributable to this. Many of the children are manifestly miserable after admission.

It is not the skilled attention which hastens their death, but rather the shortage of it.—We are etc.,

London, S.W.17. EVELYN B. LIND.
BRIAN H. KIRMAN.

Vitamin-D-resistant Osteomalacia

SIR,—In our report on "Vitamin-D-resistant Osteomalacia"[1] we remarked upon a too ready acceptance of the theory that the basic causation of this group of disorders was simply a renal tubular defect with excessive phosphate leak (the "phosphate diabetes" of Fanconi). We quoted a paper by Dr. Alan Rose[2] as an illustration. Dr. Rose has pointed out to us that he did not in his paper actually state that the sole or basic cause of the osteomalacia in his case was a primary phosphate leak, although he emphasized the occurrence of a high renal clearance of phosphate.

In fairness we must agree that we all find a high phosphate clearance in these cases, but whether this is a primary renal tubular defect or whether secondary to some other disturbance (e.g., hyperparathyroidism) is uncertain. The title of Dr. Rose's paper was "Renal Tubular Osteomalacia," which would appear to indicate a basic aetiology, although this is not specifically stated. Certainly we (Jackson and Linder) previously agreed[3] that a primary renal tubular defect provided a good explanation of the syndromes of "vitamin-D-resistant rickets and osteomalacia," but we are now less convinced, for reasons discussed in our recent paper.—I am, etc.,

Capetown, S. Africa. W. P. U. JACKSON.

REFERENCES

[1] Jackson, W. P. U., Dowdle, E., and Linder, G. C., *Brit. med. J.*, 1958, **2**, 1269.
[2] Rose, G. A., ibid., 1956, **2**, 805.
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Treatment of Habitual Abortion

SIR,—Dr. R. V. Sutton's letter (*Journal*, October 4, p. 858) and your annotation on hormone-induced sex changes (*Journal*, July 26, p. 218) suggest there may now be conclusive evidence that progesterone therapy results in the production of some abnormal foetuses, particularly in regard to the genital tract. This is not our experience.

We have recently completed a series of 50 cases using 17-α hydroxy progesterone 17N caproate ("primolut depot"). There were only two abnormalities. One baby had pyloric stenosis, since successfully treated, and the other was an anencephalic foetus stillborn at 29 weeks. We hope shortly to publish our results. Reifenstein[1] presented a comparable series to the New York Academy of Sciences on October 8, 1957. He had two abnormalities in 54 cases, neither of which involved the sex organs. Using large doses of this same hormone from the early weeks of pregnancy he had a foetal salvage rate of 69% in habitual abortion. In our own smaller series the salvage rate was just over 80%. We also agree with Reifenstein that there does not appear to be any increase in foetal abnormalities in these cases. The average total dose of long-acting progesterone given by us to these patients was 3.375 g., and in seven cases where the therapy commenced within two weeks of the first missed period the total dose approached 5 g. There were no abnormalities in these latter cases.

What are the reasons for embarking on progesterone therapy? We employ this method of treatment when we

reach the conclusion that there is no other explanation for the abortion, threatened or by habit, or where we find an arborization effect in the cervical mucus. What is the type of case? (1) A woman who has had three successive abortions as her first experiences, in the absence of genital tract abnormality, can reasonably be assumed to have a hormone imbalance—that is, progesterone deficiency. Our results support this assumption. (2) The patient who has an abortion in her first pregnancy and threatens in her second frequently has sodium chloride crystals in the cervical mucus. We use this as an indication for progesterone therapy. (3) We also use this latter method of investigation in patients who threaten to abort in their first pregnancy.

We have no experience in the use of vitamin E in habitual abortion, but are confident some of Dr. Sutton's large series of cases must have been deficient in progesterone. Perhaps this vitamin fortifies the corpus luteum, stimulates the luteinizing factor of the pituitary, or in some way accelerates trophoblastic development, thereby facilitating implantation, but, whatever the reason, this large series should be published so that others can study it. We wish to congratulate Dr. Sutton on his results and to prevail on him to give his reasons for this therapy.—We are, etc.,

Havant, Hants. JOHN FOLEY.
Portsmouth, Hants. ARTHUR C. WILSON.

REFERENCE

1 Reifenstein, E. C., *Ann. N.Y. Acad. Sci.*, 1958, **71**, 762.

A.I.D. Investigation Council

SIR,—The Eugenics Society has set up an A.I.D. Investigation Council to consider the present status and future potentialities of A.I.D.—genetic, medical, legal, and social. The Council has in mind the maintenance of a permanent committee which will at all times have a record of all available data on A.I.D. cases done in this country, with all available medical and scientific information relevant thereto. The Council would be grateful to hear from any medical practitioner with a contribution to make towards this investigation.—We are, etc.,

69, Eccleston Square, London, S.W.1. PHILIP M. BLOOM,
MARGARET HADLEY JACKSON,
Hon. Secretaries, A.I.D. Investigation Council.

Protein Anabolizers

SIR,—In the interesting and timely annotation on tissue building and protein anabolizers (*Journal*, September 27, p. 785) it is stated that: "This good effect [of testosterone therapy for bone metastases due to breast carcinoma] has been attributed to a consequent change in hormonal environment of the cancer, possibly resulting in some depression of oestrogen action by testosterone. If this is so, no good result would be expected from the use of 19-nortestosterone in this disease." Whether in fact the action of testosterone in breast cancer is due to suppression of oestrogens or not is equivocal, but I would point out that norethandrolone, in addition to its other actions, is an antagonist of oestrone-induced uterine growth in intact immature mice, with seventy times the potency of testosterone propionate. This effect of 17-nortestosterone obviously cannot be due to its androgen activity, as the androgen:anabolic ratio of this steroid is 1:15, as compared to 1:1 for testosterone propionate.[2] However, so far as I am aware, it is not yet known whether norethandrolone reduces the secretion of, or antagonizes, oestrogens in man, but adrenocortical secretion can be suppressed in man by this new steroid.[3]—I am, etc.,

Bristol. GEORGE FOSS.

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3 Brooks, R. V., and Prunty, F. T. G., *J. Endocr.*, 1957, **15**, 385.

Prevention of Lung Cancer

SIR,—I disagree with the suggestion of Mr. Leslie J. Temple (*Journal*, October 4, p. 858) that the coroner should be notified of deaths due to carcinoma of the lung in heavy smokers. He draws a parallel between such deaths and the death of a coal-miner with pneumoconiosis or a mule-spinner with cancer of the scrotum.

The latter are examples of industrial disease and as such are notifiable. There is no significant occupational or industrial link in the case of cancer of the lung, which is basically a natural disease, usually, but not invariably, associated with the habit of smoking over a period of many years. There would therefore seem to be little justification for notifying the death, and, if notified, there is no certainty that the coroner will take further action. If, however, he does hold an inquest, he may put the following questions to the medical witness: Is it possible for a non-smoker to acquire cancer of the lung? Is it possible to smoke 40 cigarettes a day for the whole of one's adult life and escape cancer of the lung? The brief answer to both questions is "Yes," a reply which can only add to the confusion which exists in the minds of the public on this matter.

Certainly our profession should spare no effort to discourage a doubting public from smoking to excess and exposing themselves to the risk of cancer of the lung (and other diseases), but the coroner's court is not, I submit, the proper platform for propaganda directed to this end.—I am, etc.,

Canterbury, Kent. G. B. FORBES.

SIR,—In the vexed question of the association of lung cancer and smoking, which has evoked much statistical analysis concerning the smoker and the preparations of tobacco smoked, and varying opinions as to their meaning, one wonders whether adequate attention has been paid to methods of igniting the tobacco.

An inveterate pipe-smoker myself, I have for decades refused to use other than a match, as the vapour from a lighter spoils the aroma throughout the entire smoke. Could it not be that pipe-smokers are more free from lung cancer than cigarette-smokers because they seldom inhale the fumes from flint-ignited lighters while those who smoke cigarettes more frequently do so? Lighter fuels consist of petrol and related substances, and, if such could be incriminated, at least a simple and rational link would be provided with the exhaust fumes of internal combustion engines, another frequently cited possible contributory cause.—I am, etc.,

London, W.1. R. R. WILLCOX.

Informing the Hospital

SIR,—Dr. Norman Gold's letter on the identification of tablets (*Journal*, October 18, p. 978) raises a host of problems. They have naturally engaged the attention of the Joint British National Formulary Committee, to which he refers and of which I am a member, but the following remarks are entirely personal in an attempt to explain some of the points involved.

First of all it must be realized that when *B.P.* preparations are mentioned in the *Formulary* (or prescribed by the doctor) it is bound rigidly by the provisions of the *British Pharmacopoeia* itself, nor can we get away from this condition by omitting the letters *B.P.* if we use the same name. And the fact is that the British Pharmacopoeia Commission, I think unwisely, has set itself against any distinctive coloration of tablets, specifically stating[1]: "The addition of colouring or flavouring agents, except where permitted in the monographs, is not official." And these permissions are hard to find. They seem to be limited to such things as tabs. mepyramine maleate ("anthisan"), promethazine ("phenergan"), or probantheline ("probanthine") where the substance is only made as a proprietary preparation and where the Commission cannot coerce the maker to its predilection to uncoloured tablets, with all their associated possibilities of confusion. It is true that in a few cases—e.g., tab. butobarbitone—the N.H.S. *Drug Tariff* does say "(may be coloured)," but this is strictly incorrect and, I think, *ultra vires*. In the same way a chemist who

provides pink tablets of stilboestrol, as he usually does, is not dispensing stilboestrol *B.P.* or *B.N.F.* and might theoretically be charged with wrongful prescribing, though not likely to incur any penalty. To give "fergon" instead of tab. ferrous gluconate is equally wrong, as fergon is red and the *B.P.* preparation is white.

The British Pharmacopoeia Commission recently replied vigorously to several curiously ill-informed criticisms of the Hinchliffe Committee, but, having participated almost *ad nauseam* in discussions on this question of distinctive coloration of tablets, I do not think that it can escape the conclusion that its present regulations tend to put a premium on doctors prescribing proprietaries and avoiding "*B.P.*" as much as possible. I need hardly say that I think this is wrong, and, as the new *B.P.* chairman was till recently the much-loved chairman of the Joint B.N.F. Committee and has heard all the arguments, we can certainly be sure that the matter will be well considered before the next edition appears.

At the same time there is much to be said for the *B.P.* It is primarily a book of standards and only secondarily one of preparations. Its aim is to maintain purity, etc., and, although the Commission contains many pharmacologists and practising pharmacists, its bias is more towards maintaining accuracy and stability of products than their sale in shops or use in medicine. This is exacting enough on its own, and it would probably be a mistake to try to saddle it with a lot of manufacturing details as well.

Besides the question of distinctive coloration there are possibilities of circumventing the *B.P.* regulations by differences in size and shape (though even here the *B.P.* Appendix XXI C sets strict diameters for its tablets, again excluding proprietaries) or by impressing specific dots, letters, lines, or other markings. Dr. Gold says that his collection contains 49 such specimens, but Bayer's latest handbook gives 33 distinctive marks, while I.C.I., Ciba, and others have long employed similar devices, so I fear his collection is far from complete. It would, I think, be impossible for our hardworking B.N.F. Committee (which for some of us involves about three half-days every month for 9–12 months for each edition) to correlate all these markings and devise new ones for every fresh drug, many of which will never get widely used in this country.

I am sure, however, that this matter is one worthy of serious attention, and that at present it falls between many stools. The B.P. Commission is aloofly concerned; on the B.N.F. we get nearer to the problem if not to the answer; manufacturers and dispensing chemists see their different aspects of it; while hospitals, doctors, and the Government, as the chief consumer, are all involved. One or two conferences of all parties concerned might at least lead to clarification of the main issues, and if they all came with the desire to find a solution and not hold their present ground some progress might be made in alleviating an ever-growing problem.—I am, etc.,

Winsford, Cheshire. W. N. LEAK.

REFERENCE

[1] *British Pharmacopoeia, 1958*, p. 655. London.

SIR,—The letter from Dr. N. Gold (*Journal*, October 18, p. 978) suggests that there should be a system for identification of drugs. There is an excellent "Tablet and Drug Identification Guide" published by the *Chemist and Druggist* which we find extremely useful in our hospital.—I am, etc.,

St. Olave's Hospital, Lower Road, London, S.E.16. JANE M. FULLERTON.

Convulsions and Epilepsy

SIR,—I was most impressed by the clarity and the good sense of the W.H.O. technical report on juvenile epilepsy.[1] It is because of its excellence in all these respects that I feel moved to protest on a matter of nomenclature. There is a trend among the experts in this field to accept all convulsions as synonymous with epilepsy, and in this report "epilepsy refers to all clinical forms of attacks that are known by electroencephalographic (E.E.G.) and other investigations to be accompanied by the characteristic electrical activity of the brain recognized as epileptic." This definition may be scientifically accurate, but if every convulsion is going to be labelled as epilepsy it will prove embarrassing to the general practitioner who has an important role to play in the diagnosis and management of this disorder. To him epilepsy connotes an episodic disease which can in most cases be controlled by anticonvulsants. The epileptic is thus either a person who has *repeated* fits of one kind or another, or who needs continuous treatment to keep them under control. The occasional fever fit is not considered to be epileptic, although it is appreciated that in a minority of cases such attacks are the beginning of chronic epilepsy.

Our patients accept the dictionary definition of epilepsy as "a nervous disease in which the patient falls to the ground unconscious, with spasms and foaming at the mouth." It is a term that conjures up the worst possible picture in the mind of the distraught mother of a child who has had a convulsion of any kind. Simple arithmetic shows that fever fits and epilepsy are not in fact the same thing. The report suggests that 6% of the population at one time or another have a convulsive episode. The present accepted estimate for chronic epilepsy is 3–4 per 1,000 of the population. This means that only one in every 15–20 people who have an occasional convulsion becomes a chronic epileptic, and of course only a small proportion of these chronic cases (my own figures suggest 12%) deteriorate: the majority, with their fits well controlled, are gainfully employed. My plea, in which I think most general practitioners will support me, is that scientific accuracy should be met by applying the term "convulsive disorders" to all epileptiform attacks and reserving the term epilepsy to describe the chronic case with repeated attacks either occurring or prevented by therapeutic measures. This differentiation will help the family doctor when he has to reassure the parents of a child who throws the occasional fever fit. While I am all in favour of early and full examinations of such cases by experts with all modern equipment, each case must be judged on its merits, and scientific progress must not be made at the expense of increasing parental distress and anxiety.—I am, etc.,

Ibstock, Leicester. C. A. H. WATTS.

REFERENCE

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1957, No. 130.

Beds for the Aged

SIR,—Dr. K. M. Tankard can rest assured that the Sunderland Geriatric Unit deals with all the cases he mentioned in his letter to the *Journal* of October 18 (p. 979). He is welcome to visit the department if he would like to see for himself.—I am, etc.,

Sunderland. E. WOODFORD-WILLIAMS.

Buzzers for Bed-wetters

SIR,—The recent correspondence in the *Journal* has been concentrated on the physical methods of treatment of enuresis. It seems to regard it as due to some physiological dysfunction of the bladder and to ignore the psychogenic factors involved. Enuresis is a source of much unhappiness both to the child and the parents. It is the only symptom which children are ashamed of. The child frequently lacks the support and sympathy which he so desperately needs from his parents, who more often than not administer severe punishment, which nowadays tends to be mental rather than physical. So many parents adopt an attitude of hopelessness accompanied by nagging that the child becomes morose and introverted, and lives his life sodden, sore, odorous, and miserable. The anxiety accentuates the condition. Together with it goes the slacking at school and loss of self-confidence. Some psychogenic factors may complete the vicious circle—a new baby in the family, temporary or permanent loss of a parent, too anxious and worrying parents, illness, and a variety of other causes. Each treatment tried which fails to give permanent results only undermines more the patient's confidence.

The first thing to do, therefore, is to build up the child's confidence in himself and to get the parents to accept the symptom and to understand that their attitude is important. There may be something frightening and worrying the child at home or at school, and the enuresis may be a defensive

mechanism. This has to be discovered and dealt with and the patient's security restored. If the patient can be given confidence that the symptom can be controlled by himself, the anxiety ceases.

Hypnotherapy is by comparison more effective than any other therapeutic method in helping these patients. It makes it possible to deal with the fear, anxiety, and worry and to help them to fight against the habit irrespective of the factors causing it, and to restore their self-confidence. One hears very often from a child after a few sessions of hypnosis, "I don't seem to worry any more: even if I wet my bed I won't worry." By improving the child's confidence in himself one gives him back his self-respect, and one part of the vicious circle is broken This, coupled with the explanations to the parents, often serves to break the remaining part of the circle. It usually results in a considerable improvement in the child's school progress.

The aim of the buzzer is to establish a conditioned reflex. It acts as soon as the patient passes some urine. It immediately lets the whole household know about it and it makes the unfortunate sufferer still more ashamed and worried. It does not help him to understand and deal with the underlying factors causing his complaint and to break the vicious circle. Dr. Clifford Allen (*Journal*, September 27, p. 799) mentioned in his letter about strong suggestions which he uses when treating enuretics with pituitary snuff. It would be interesting to try some cases giving them similar suggestions but with an inert snuff and see the results.—I am, etc.,

London, S.E.25. A. FRY.

Coloured Immigrants

SIR,—Racial problems will not be solved by Dr. J. Tudor-Hart's denying (*Journal*, October 18, p. 974) the need for "more research into the results of race-mixing" (*Journal*, October 4, p. 843). Since almost every known species of animal with a wide distribution has differentiated into distinct geographical races, it is hardly surprising that man, who has the widest distribution of them all, should have done the same. A recognition of the differences, physical, mental, and cultural, between the primary races of mankind should go some way towards dispelling the nonsense talked about people simply happening to differ from each other in the colour of their skin and need do nothing to foster any idea of superiority or inferiority. A respect for other peoples' race might be a better basis for mutual co-operation than the rather doubtful compliment of trying to persuade a negro that he is the same as a white man. It has never been suggested in your columns that research should be bedevilled by politics and sentiment as was the case with the German race-scientists and the Russian plant-breeders; provided it is carried out with scientific integrity it can do no more than arrive at the truth.

As to the second problem Dr. Tudor-Hart mentions, it seems fairly obvious that too much money, too little work, no discipline, and less religious training will inevitably breed a generation of cowardly louts.—I am, etc.,

Morcton-in-Marsh, Glos. E. H. EASON.

Anterior Spinal Artery

SIR,—In their report of a case of anterior spinal artery syndrome Mr. A. Davies, Dr. B. Solomon, and Mr. A. Levene (*Journal*, September 13, p. 654) discuss the anatomy of the arteries of the spinal cord. They state that the anterior spinal artery is virtually an end artery receiving significant collaterals only at the level of T1 and T11. This description is certainly not in agreement with the classic accounts of the circulation of the cord by Adamkiewicz[1] and Kadyj[2] nor with more recent work.[3–5] The anterior spinal artery presents the appearance of an anastomotic chain made up of ascending and descending rami from a comparatively small number of anterior radicular arteries. In a series of 68 specimens examined by myself these latter vessels were found to range in number from 2 to 12. They were found distributed throughout the length of the cord, but were most numerous in the cervical and thoracolumbar regions and were usually absent from the midthoracic region. The largest anterior radicular artery, the arteria radicularis magna of Adamkiewicz, was found anywhere between T6 and L3.—I am, etc.,

Manchester, 13. J. B. D. TORR.

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2 Kadyj, H., *Anat. Anz.*, 1886, **1**, 304.
3 Suh, T. H., and Alexander, L., *Arch. Neurol. Psychiat. (Chicago)*, 1939, **41**, 659.
4 Torr, J. B. D., *Lancet*, 1957, **2**, 146.
5 —— M.D. Thesis, 1957, Manchester University.

"On Call to a Nation"

SIR,—In this T.V. documentary (see *Journal*, October 25, p. 1053) a G.P. is consulted by a young man suffering from headaches. He hands him a form without further questioning and tells him to go to an optician to get some glasses. He made no attempt to inform the patient that he could have a medical eye examination or one from an optician.

Fortunately many G.P.s realize that a member of their own profession can advise on the medical as well as the optical aspects of the case, and is in the best position to decide whether glasses are likely to relieve symptoms or not. They consider a medical test preferable if the patient has never had glasses before, in children, and of course if any pathological condition is suspected. However, there are quite a number of doctors who deliberately send their cases to opticians, and evidently this T.V. doctor is one of them. I feel that it is a pity that he should have appeared before the public as a champion of the ophthalmic optician in preference to recommending the patient to an ophthalmic medical practitioner. I hope that the T.V. authorities will grant an interview with a member of the N.O.T.B. Association so that the public will be furnished with the true facts.—I am, etc.,

London, W.14. C. WATNEY ROE.

Premonition of Death

SIR,—The famous Nostradamus, who died on July 2, 1566, knew in the night about his death and at the end of June of the same year wrote with his own hand, "Hic prope mors est." In the evening of July 2 he told his disciple, "you will not see the living at the new dawn."[1]—I am, etc.,

London, N.W.11. N. PINES.

REFERENCE

1 Ruir, E. M., *Nostradamus*, 1948, p. 99. Paris.

Rhymed Review

SIR,—

How pleasant to the eye and mind
A lucid book review to find,
So apt and pithy with its rhyme,
Saving a column's reading time.
Such verse appropriately used
Would brighten those who have accused
The *B.M.J.* as dull and glum,
Too vague, prolix, and wearisome.
Then with your grace may we all hope
That others follow Zachary Cope.[1]

—I am, etc.,

Basingstoke. I. ATKIN.

REFERENCE

1 *Brit. med. J.*, 1958, **2**, 958.

POINTS FROM LETTERS

Back-to-School Syndrome

Dr. J. SAPERIA (London, E.10) writes: Recent entrants to general practice may not be aware of the mothers' "back-to-school syndrome." It arises in those who rush to and from school with their young four times a day. Tiredness and recent loss of weight are the presenting symptoms. A rapid cure results from the organization of a rota, or leaving the child to school dinners.

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Obituary

J. A. GUNN, C.B.E., M.D., D.Sc., F.R.C.P.

Professor J. A. Gunn, who died in Oxford on October 20 at the age of 76, was the professor of pharmacology in the University of Oxford from 1917 to 1937, director of the Nuffield Institute for Medical Research from 1935 to 1946, and Nuffield professor of therapeutics from 1937 to 1946.

James Andrew Gunn was born at Kirkwall in Orkney on January 26, 1882, and was educated there until he went to Edinburgh University. There he graduated M.A. in 1901, B.Sc. in 1903, and M.B., Ch.B. in 1905, proceeding M.D. in 1907 (gold medallist) and D.Sc. in 1909. Having distinguished himself greatly in scientific subjects, winning numerous prizes and scholarships at Edinburgh, he began to study pharmacology in the laboratory of Sir Thomas Fraser, and he continued in this field until his retirement. In 1912 Gunn was appointed reader in pharmacology at Oxford, and in the same year he was awarded a Beit research fellowship. After a period of service in the R.A.M.C. in the first world war, he was appointed professor of pharmacology at Oxford in 1917, occupying that chair until 1937, when he became the first Nuffield professor of therapeutics at Oxford. The degree of D.M. was conferred on him in the following year. When he retired in 1946 he was appointed emeritus professor. Besides many contributions to medical and scientific journals, Professor Gunn was the author of *An Introduction to Pharmacology and Therapeutics*, which reached its 9th edition in 1958. He also edited Cushny's textbook on *Pharmacology and Therapeutics* and Whitla's *Pharmacy, Materia Medica, and Therapeutics*.

[*Elliott & Fry*

Professor Gunn was a past-president of the Oxford Medical Society and of the Section of Therapeutics of the Royal Society of Medicine. At Annual Meetings of the B.M.A. he first held office as vice-president of the Section of Physiology and Pharmacology in 1920, and was president of the Section of Pharmacology and Therapeutics in 1927, 1932, and 1936. Elected a member of the first Pharmacopoeia Commission, set up by the General Medical Council in 1928, he later became chairman of the Commission, being appointed C.B.E. for this work in 1947. He also was a member of the B.M.A. subcommittee on the British Pharmacopoeia Commission and of the Committee on the Relation of Alcohol to Road Accidents. At the League of Nations in Geneva he served on the Committee on Narcotics. An honorary member of the Pharmaceutical Society, he was for some years a member of the council of that society. In 1935 he gave the Dohme lecture at Johns Hopkins University and four years later the Oliver-Sharpey lectures at the Royal College of Physicians in London, of which he was elected a Fellow in 1931.

J. H. B. writes: Professor Gunn's chair was very suitably attached to Balliol College, which has always had a strong Scottish connexion, and he was well known and greatly liked throughout the university. Extremely modest, with a cheerful and humorous disposition, he spoke quietly in a slightly husky voice which was full of charm. He had the appropriate degree of professorial absentmindedness, and perhaps the best-known story of his early days at Balliol is how one evening he had gone by mistake to dine in the hall of St. John's. Balliol has long had a reputation for high thinking but austere living, and Gunn, halfway through his plate of soup, looked up and said, "Surely this cannot be Balliol!"

The grant of money available for running a department of pharmacology was very small in the early years, and for such a situation Gunn was an ideal person. He showed great ingenuity in devising simple experimental methods for which expensive equipment was not required, and built up a series of exercises for a practical class with very little expenditure. When the Sir William Dunn trustees invited the heads of some of the departments to submit proposals for expansion, Gunn's proposal, drawn up with a natural Orcadian sense of economy, was the one which they liked best, and their first intention was to build a school of pharmacology. Sir Walter Fletcher then became very active and persuaded them to build a school of pathology, having first secured Gunn's agreement to take over the existing pathology building for pharmacology.

A great blow which Gunn suffered was his very serious illness about 1925, when he had a streptococcal infection and lost his sight in one eye. At one stage the decision had been taken to remove the eye, but on the morning on which the operation was to be performed his small son, coming in to see him, noticed that his eye was better, and as a result the eye was left in its place. There can be little doubt that this illness compelled him to reduce his scientific activity for some years.

Gunn was a very attractive lecturer, both because of his voice, to which it was a pleasure to listen, and because of his skill in presenting his matter and of the care he took in making it interesting. The same success which he had as a lecturer attended his writings. In this respect his *Introduction to Pharmacology and Therapeutics* was a model, for his style was full of grace. On the title-page appeared a quotation from Oliver Goldsmith: "Were angels to write books, they would never write folios," and this showed how clear a grasp he had of the art of teaching.

The main line of research followed by Gunn was laid down by an interest in adrenaline which he gained as a pupil of Schäfer, who had gone to Edinburgh in 1899. Gunn investigated the action of the amines which formed a series beginning with phenylethylamine and ending with adrenaline. In his Oliver-Sharpey lectures given in 1939 he gave an account of this work, which is of greater interest to-day than it has been in the intervening period. In 1914 Bry had shown that phenylethylamine had a central excitatory action because of its effect on respiratory rate and in causing convulsions. In 1932 Gunn with his colleagues Epstein and Virden observed that this central action was almost abolished when an $-OH$ group was attached to the ring in the *para* position (forming tyramine) and disappeared altogether when a second $-OH$ group was added in the *meta* position (forming dopamine). While the introduction of $-OH$ groups removed the central action, Gunn showed that the introduction of an $-OCH_3$ group restored it, whether the restoration was in the *para* or *meta* position. He also showed that the central action again disappeared when two $-OCH_3$ groups were introduced. He concluded that central stimulation was likely to be found when the benzene ring was unsubstituted, when it contained a methoxy group or a methylene dioxy group. The compound which was most active centrally was methylene dioxyphenylisopropylamine.

The interest of this work to-day springs from the knowledge that the pathway of the breakdown of adrenaline in the body is through the methylation of the $-OH$ group in the *meta* position in the ring, and that the enzyme which effects this methylation is also present in the brain. Gunn's own interest in his experiments lay in the hope of finding a pressor agent more stable and more prolonged in action than adrenaline or tyramine, but lacking the central action of amphetamine or ephedrine. Starting from phenylethyl-

amine he proposed the introduction of a $-OCH_3$ group in the *meta* position and an $-OH$ group in the *para* position to neutralize the central action. Then he proposed substituting a $-CH_3$ group on the α carbon of the side chain to render the substance immune from attack by amine oxidase. This compound was synthesized by Sir Robert Robinson and did indeed fulfil some of the hopes. Its duration of action was five times as great as that of adrenaline, and its toxicity was only one-sixth that of amphetamine. In later papers he studied the cyclohexylalkylamines, and the effect of introducing unsaturated linkages in the side chain.

Professor Gunn was a wise and learned man, courteous and fair to all who knew him, and a sympathetic examiner of medical students. He was regarded with sincere affection and great respect. In his home life he was blessed in having a devoted wife, who survives him, together with a daughter and two sons. His third son was killed in the fighting in Italy.

D. B. McGRIGOR, O.B.E., M.B., Ch.B., D.M.R.E.

Brigadier D. B. McGrigor, formerly consultant radiologist to the Army, died in Colchester Hospital on October 22, aged 73.

Dalziel Buchanan McGrigor was born on January 20, 1885 at Torry, Aberdeen, the son of James McGrigor, a consulting engineer who practised in Calcutta. Educated at Robert Gordon's College, Aberdeen, he went on to the University of Aberdeen to study medicine, graduating M.B., Ch.B. in 1907. After holding a resident hospital appointment in Perth, he entered the R.A.M.C. in 1907 and, having qualified with distinction as a specialist in electrical services at the Indian *X*-ray Institute, he served in India from 1909 to 1914. During the early part of the first world war he was on active service in France, with the Indian Expeditionary Force, in charge of No. 1 field *x*-ray section. Returning to India in 1916, he was appointed D.A.D.M.S. of the 9th Indian Division in 1918. In the following year he was promoted major and appointed O.B.E. From 1919 to 1920 he was D.A.D.M.S. of Northern Command at York. Having taken the D.M.R.E. of Cambridge in 1920 he became specialist in charge of radiology at Queen Alexandra Military Hospital, Millbank, and lecturer to the Royal Army Medical College. Retiring from the R.A.M.C. in 1927, he was appointed adviser and examiner in radiology to the Army Medical Services. In the same year he went on a visit to Army Medical Headquarters in Washington to inspect the radiological services there. Four years later he carried out a similar visit of inspection at Army Medical Headquarters in Paris while attending the Third International Congress of Radiology as a member of the British delegation. In 1939 McGrigor was recalled from the reserve, and as an adviser in radiology to the Army Medical Services he organized the Army School of Radiology. In 1941 he was promoted brigadier, and in the following years undertook tours of inspection in N. Africa, the Middle East, and France. Continuing to serve as consultant radiologist to the Army Brigadier McGrigor finally retired in 1952, when 67 years of age. As a result of his work during the second world war he was awarded the Legion of Merit by the United States Government, the Czechoslovak Military Medal (1st class), and the Polish Silver Star.

Brigadier McGrigor was a member of the executive committee of the British Institute of Radiology for many years, and was president of the Institute from 1939 to 1942. In 1946 he received, jointly with Lieutenant-Colonel Eric Samuel, the Roentgen Award of the Institute. In 1935 he was vice-president of the Section of Radiology and Radiotherapeutics at the Annual Meeting of the B.M.A., held in Melbourne that year. Well known and popular among American radiologists, he was elected an honorary fellow of the American College of Radiology in 1952. He was also an honorary fellow of the Society of Radiographers.

Brigadier McGrigor married Dorothy Macgregor Drysdale in 1912, and she survives him with one daughter and two sons, Dr. A. B. McGrigor, senior registrar in the department of diagnostic radiology at University College Hospital, and Mr. R. B. McGrigor, senior registrar in the department of surgery at St. Bartholomew's Hospital.

We are indebted to Dr. R. BOULTON MYLES for the following appreciation: It was at the Royal Army Medical College at Millbank in 1921 that I first met "Mac." He was then the officer in charge of the *x*-ray and electromedical departments of the Queen Alexandra Military Hospital, and lecturer in radiology at the College, so to me, a junior officer on a promotion course, he was a big man. And he remained so, big in knowledge as well as stature, and —how important this—big in heart. The fact that he was a senior officer never obtruded itself, which was one of the reasons why he was such an excellent teacher, as I was to discover later when I was privileged to attend the specialist course under him. Very quick to size up a student's general outlook and possibilities, he seemed to know exactly when to be strict and when to relax, when to be present and when to leave us to work out our problems on our own initiative. Before the end of the course I found that in addition to meeting a first-class teacher I had made a new friendship—one which has now been broken by the only possible means. When he retired from the Army he did not sever his connexions with Army radiology, but remained as secretary and mainspring of the Army *X*-ray Advisory Committee until it was finally disbanded after the war. Meanwhile, though not practising as a radiologist, he was taking a more important place in medical radiology outside the confines of the Services. He was treasurer of the British Institute of Radiology for ten years, and relinquished the office then at his own request because he thought it was time for a younger man to take over. The Institute signified its approval by making him president instead, and keeping him there for three times the normal term of office.

On the outbreak of war in 1939 he was immediately called to the War Office to correlate radiological services in the Army—in other words, to put into practice the fruits of his previous labours on the *X*-ray Advisory Committee. The Army was indeed fortunate to have at its disposal one whose hobby ever since he left the active list had been the study of medical radiology in its broadest aspects, and undoubtedly with particular reference to the possibility of just such an emergency. His knowledge of the technical problems involved and his close liaison with the designers and manufacturers of the essential apparatus enabled him to take the duties of an onerous post in his stride, so that he appeared always to have time for personal consultation regarding the numerous problems which arose. Since the war his radiological activities had lessened, not through loss of interest, but because, in his own words, "We old men should step aside and let the others carry on." Nevertheless, he remained a staunch supporter of the British Institute of Radiology and attended its meetings with great regularity. Another of his important side-lines was his interest in the R.A.M.C. Officers', Widows', and Orphans' Friendly Society, to which he devoted a great deal of time and thought for many years. Its strong position and smooth running are due in no small measure to his efforts. Mac was, in the best sense of the phrase, a good mixer, and he had friends everywhere. He missed no opportunity of visiting hospitals and *x*-ray engineering works in Britain and in most parts of the world, and wherever he went he was always asked to return. Only last year he toured Canada and the U.S.A. again at the invitation of the American radiologists, who had a very high opinion of his qualities. In addition to being universally popular outside, Mac was very much a family man, and we who are going to miss our occasional contacts with him realize how much more he will be missed at home. He was a great personality, of a type which we can ill afford to lose.

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[1] March 1955. p.62
[2] C.R. Soc. Biol. (Paris). 1948. 142. 819

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W. S. FLOWERS, M.B., Ch.B.

Dr. W. S. Flowers, formerly a medical missionary in China, died at Harrogate on September 26. He was 60 years of age.

Wilfred Stephen Flowers was born on May 27, 1898, and studied medicine at Leeds University, where he graduated M.B., Ch.B. in 1925. He had already been trained in missionary work, and after graduation went to China as a medical missionary. He left that country in 1939, after being ill-treated by the Japanese in occupied China, and was medical superintendent of the Wharncliffe Hospital, Sheffield, for two years. He then went back to China to take charge of a British Red Cross Hospital on the Burma Road. He also assisted the Chinese Government in its task of medical reconstruction after the defeat of the Japanese in the second world war. In September, 1948, he was among the last to leave Tsinan before that city was captured by the Chinese Communists, and the time of his escape coincided with a breakdown in health, which caused him to give up missionary work abroad. At home he became secretary of the Yorkshire Association for the Care of Cripples, an appointment he held until his death. He leaves a widow and two sons, both of whom are in the medical profession.

R. B. writes: Dr. Wilfred Flowers, "Blossom" to his fellow residents at the General Infirmary at Leeds, had first trained at Rawdon Baptist College in preparation for his work as a medical missionary before proceeding to Leeds University for his medical training. While a student he was a member of the universities debating team which toured South Africa in 1924. After graduation he embarked on his life's work in China. He established and was in charge of the Missionary Hospital at Chowtsun, and had a difficult time when it became Japanese occupied territory. After furlough in England he returned to China in 1942 as leader of a British Red Cross unit. He was the first representative of the Allies to enter the Japanese internment camp at Shanghai with news of deliverance. In 1946 he accompanied Sir Clutha Mackenzie on a tour of China primarily concerned with the "non-sighted." In 1948, when the Communists were coming into power, he was about to board an aeroplane to go and see Mao-Tse Tung about the rehabilitation of missionary hospitals, when he had his first coronary attack. Unable to continue his missionary work, he took over the secretaryship of the Yorkshire Association for the Care of Cripples and established training centres for cripples, first at Harlow Grange and then at St. George's, Harrogate.

WILLIAM DAVIES, M.R.C.S., L.R.C.P.

Dr. William Davies, who was medical superintendent of the Sully Hospital, Glamorgan, from 1935 to 1951, died on September 28 at the age of 73.

William Davies's life was very much a triumph over adversity. Starting to earn his living at a very early age, he found himself forced, at the age of 26, to give up his work or risk the possibility of blindness. Deciding to become a teacher, he went to Carmarthen to prepare himself for his new profession. There a friendly medical practitioner recognized his abilities and persuaded him to switch to medicine. While studying in London he came under the influence of Sir Robert Hutchison, and this period of hero-worship did him much good and was to shape his attitude towards his profession. One could detect the insistence on realism, the tendency to "debunk," and the thoughtful approach to problems. This attitude had been superimposed on a nature that was essentially kindly, a nature marked by a desire to help and with an instinctive knowledge of the psychology of his patients. Shortly after qualifying M.R.C.S., L.R.C.P. in 1918 he went to Brecon, and it was from there that he was induced to join the staff of the newly opened South Wales Sanatorium at Talgarth. The appointment was a temporary one, but he soon found that tuberculosis was to be his life's work. He never left the service of the King Edward VII Welsh National Memorial Association.

In 1924 he was invited to open the recently adapted Cefn Mably Hospital, near Cardiff. At Talgarth he had helped in the rehabilitation of tuberculous patients, but at Cefn Mably Hospital he had to treat patients in a more active stage of the disease. During the eleven years he spent there he extended his knowledge of his subject by visiting Switzerland to see the treatment of bone tubercle by heliotherapy and then to Paris and Berck-Plage to see the treatment by immobilization in plaster. Before completing his stay in Cefn Mably he was appointed to the Sully Hospital, which was in course of construction. He supervised the construction and equipment of the hospital, and during the year before completion his job was a full-time one. The appointment was a unique one and was fully justified by the saving in mistakes, in time, and in money. He had time to consider the different types of equipment and to make a sound judgment. There was a rare understanding between Davies and his chief, Dr. Dan Powell. Their wish to make the hospital up to date was fulfilled. All this was not accomplished without sacrifice. In addition to his eye trouble he had been plagued by migraine and by sciatica—the latter a reminder of his work in earlier days. His great interest was in radiology, and he specialized in this work. Perhaps the threat to his eyesight made him see in *x* rays a third eye to help him in his work. It was a source of wonder and amusement to his patients that he recognized them by screening them. At Sully he set the pattern and helped to raise it to the international status it now enjoys. He retired in 1951, but, being much too interested to stop work, he joined the Pneumoconiosis Panel, where his previous knowledge of mining was a great asset. His death is a great loss to those who knew him, and sincere sympathy is extended to his widow and children. His son and daughter have followed his example and are members of the medical profession. It is perhaps fitting that we should remember this well-beloved Welshman by a quotation from the language he loved so much. It is a proverb that sums up his life: Adfyd a ddwg wybodaeth, a gwybodaeth ddoethineb (Adversity brings knowledge and knowledge wisdom).—H. A. R.

J. A. MORTIMER, M.D., F.R.C.P.Ed.

Dr. J. A. Mortimer, consulting surgeon to the Glasgow Eye Infirmary, died at Law Hospital, Carluke, on October 10. He was 71 years of age.

John Alexander Mortimer was born on May 16, 1887, the son of an Edinburgh law agent, and was educated at George Watson's College and at Edinburgh University. After an undergraduate career of some distinction, he graduated M.B., Ch.B. in 1909. Two years later he proceeded to the M.D. and was elected a Member of the Royal College of Physicians of Edinburgh, being admitted a Fellow of the College in 1943. After graduation he was an assistant in general practice in Dumfries, before beginning his specialist career at the Bradford Royal Eye and Ear Hospital, where he remained until 1921. During the first world war he served in the R.A.M.C. as an ear, throat, and nose specialist at Étaples. In 1921 he gave up the throat and nose side of his practice to become school oculist to the Lanarkshire education authority, and a year later he was admitted to the staff of the Glasgow Eye Infirmary, where he became a full surgeon in 1935. After his retirement from the hospital in 1947 he carried on his school work in Lanarkshire until shortly before his death. In addition to these appointments, he was a certifying surgeon to the Mission to the Outdoor Blind in Glasgow. He carried on a private practice in Lanarkshire, where his name was well known. Taking a prominent part in the work of the West Church of Hamilton, he was for over 30 years an office-bearer there. He was a very good and enthusiastic golfer. A man of pawky humour, he never lost his east coast accent, nor his command of the Doric. His opinions of all forms of government were

freely expressed in terms which left the politicians—medical or otherwise—in no doubt as to his opinions. In spite of these strongly and vigorously expressed views he was, withal, a kindly man, and his patients and colleagues could see the kindly man under the rough exterior.

W. A. A. FAMUYIWA, M.B., Ch.B.

Dr. W. A. A. Famuyiwa, a young Nigerian who had been in the medical profession only a few months, was killed in a car accident near Berwick-on-Tweed on October 19. He was 35 years of age.

Wilson Adelola Alade Famuyiwa was born on January 18, 1923, and studied medicine at St. Andrews University, where he graduated M.B., Ch.B. last July. At the time of his death he held an appointment at the Bridge of Earn Hospital.

A. P. writes from Dundee: The tragic and untimely death of "Famy" as a result of a car crash came as a great shock to those of us who were privileged to have experienced his friendship. His cheerfulness was infectious—he enjoyed life to the full, and those with whom he was in contact enjoyed it with him. His radiant smile was disarming and a source of delight to his colleagues, nursing staff, and patients. He was always ready to perform acts of kindness and service to his friends; he never bore a grudge, nor had he a harsh word to say to or about anyone. "Famy" was a sincere and good man, and a fine ambassador for Nigeria. His death is a great loss, not only to his friends in Great Britain but also to his own people, among whom he ultimately intended to practise.

H. E. HODGE, M.B., Ch.B.

Dr. H. E. Hodge, better known as Merton Hodge, playwright and actor, died recently at Dunedin, New Zealand, at the age of 54.

Horace Emerton Hodge was born at Gisborne, New Zealand, on March 13, 1904, and was educated at King's College, Otahuhu, at Auckland University College, and at Otago University, graduating M.B., Ch.B. from the University of New Zealand in 1929. After house appointments at the Dunedin, Wellington, and Auckland Hospitals, he came to Britain to take a postgraduate course at Edinburgh, and while there wrote *The Wind and the Rain*, a play which subsequently ran for 1,000 performances in London. On leaving Edinburgh he served in the R.A.M.C. for two years, and this was followed by a further year as an anaesthetist at St. George's Hospital, London. In 1935 he gave up medicine to take his play to New York. For the next four years he concerned himself almost solely with authorship and dramatic work. He anglicized the American play, *Men in White*; he wrote his second play, *Grief Goes Over*, which was presented in London in 1935; and in 1936 he published *The Wind and the Rain* as a novel under the title of *The Island*. Three other plays came from his pen up to 1939, when, on the outbreak of the second world war, he returned to London and to medicine. From 1939 to 1944 he was on the staff of the Camberwell House Hospital for Nervous Diseases. After the war he was in practice in London for a few years, and finally in Dunedin. He was unmarried.

HENRY WALLACE-JONES, M.Sc., M.D., F.R.C.P.

The obituary of Dr. Henry Wallace-Jones was printed in last week's *Journal* (p. 1045).

E. N. C. writes: I had the privilege of working with Henry Wallace-Jones on and off for over 35 years. When he was assistant physician to Professor John Hay I acted as their house-physician and later medical registrar. No one could have been more kind to a young man. He was able in a clear and simple fashion to give excellent clinical instruction to his students and younger staff, and always in a spirit of toleration and understanding of our ignorance. As time passed and Professor Hay retired, Wallace became head of the heart clinic, which had been founded by his chief, a disciple of Mackenzie: he was therefore in direct succession to the pioneers of British cardiology. At this time I became his assistant physician and was again impressed by his quiet modesty and the sense of happiness which he spread among all of us who had the privilege of working with him. Apart from his outstanding clinical ability, he had an inquiring type of mind, with a great zest for the mastery of the modern instruments of cardiology. If his active life had been prolonged 10 years I am sure he would have been in great sympathy with the modern highly scientific approaches to the problems of heart disease. But in his own day he made the best use of the polygraph, the electrocardiograph, and the radioscope. He did not write extensively, but his publications are such as to have stood the test of time. When he retired from the Royal Infirmary, to which he had loyally given the whole of his professional life, he sought the sunnier climate of South Africa and continued for a little while to practise as a consulting physician. Once a year he came back to England, and only recently we had the pleasure of a short visit by him to the regional cardiac centre. He still had family interests in Liverpool, where one of his sons practises as a radiologist, and I know that much of his retired life was devoted to the furtherance of his children's plans. He was a happy man by disposition, and his devoted and charming wife helped him to spread this happiness to all those who had contact with him. There must be many outside the Royal Infirmary who will mourn his loss but who will be grateful for their pleasant associations with him.

CHARLES M. FRIER, M.B., C.M.

The obituary of Dr. Charles Frier was printed in the *Journal* of October 11 (p. 921).

J. B. A. writes: With the death of Dr. Charles Frier the people of Grantham and its surrounding villages have lost an old and a trusted friend. When he retired three years ago he had been in active practice in Grantham for sixty years. He will be missed by a host of patients who had also become his friends, and though his manner at times was abrupt they knew they could trust him. He was typical of the best of the general practitioners of his generation, being efficient in all branches of medicine and surgery, including gynaecology and ear, nose, and throat work. He had his own *x*-ray apparatus, which he managed himself. He also did refractions. In fact, he was both "Jack" and "Master" of all trades. On coming to Grantham he purchased a small declining practice, and when he retired he was the senior partner in a large firm of six principals. One of his lifelong interests was the welfare of children, and for years he was the secretary of the local branch of the National Society for the Prevention of Cruelty to Children. He was the treasurer and founder of a local fund, known as Dr. Frier's Crippled Children's Holiday Fund, whereby about thirty children—not now, I am glad to say, all cripples—are sent to the sea each year for a fortnight. This year was the first year he was unable to be there in person to see them off. For many years he was an active member of the local bench and chairman of the juvenile court, where his wisdom and understanding were of great value. He was a most generous person, and his name figured prominently in all charitable appeals. I was told a story the other day by an old district nurse, which is typical of "The Old Man." One day, years ago, she saw his bicycle outside a cottage in a village five miles away at about 8 a.m. She went in and found Dr. Frier on his knees setting and lighting the fire. The patient upstairs was about to have a baby, and there was no hot water and no help. He was, of course, looked up to by all the profession in Kesteven. Anyone in trouble or difficulty always turned to him for advice and help, which was unfailingly given.

F. J. J. writes: Dr. Charles Frier was regarded for many years as the doyen of the medical profession of the Kesteven

area of Lincolnshire. He came to Grantham some sixty years ago, and when he retired a few years ago the partnership had risen to one of six doctors. He represented the old school, and his Gladstonian manner of dress lent dignity to his appearance at the meetings of the Representative Body, at which he was a well-known figure. His rugged personality deceived a little, but hid a kindly character. Always ready to help, his charitable acts were known to only a few. Apart from his vast medical knowledge he possessed considerable surgical skill in his younger days and undertook operative procedures under conditions that would test the courage of a modern surgeon. He had untiring energy, and up to the age of 70 would work until the early hours of the morning. He retired from practice only a few years ago, though he continued to visit a few favourite patients. He was one of the early members of the Kesteven Division and was its representative in the Representative Body, alternately with the Holland Division, before the two Divisions were granted separate representation. He continued to serve in this capacity for nearly forty years, until indifferent health made it difficult for him to attend. A former president of the Lincolnshire Branch and chairman of the Kesteven Division, his knowledge of B.M.A. affairs and medical politics was phenomenal. He acted as secretary of the panel committee from its inception and of its successor, the local medical committee, for some years, and he was treasurer of the latter until his death. During the second world war he was for a time chairman of the local medical war committee. He served on the staff of the Grantham Hospital for twenty-five years until 1948, and held the appointments of public vaccinator and Poor Law medical officer. He instituted a local charity for providing seaside holidays for sick children. As a token of esteem the Lincolnshire Branch of the B.M.A. presented him with a pair of antique candlesticks some ten years ago, and his election as a Fellow of the Association this year gave him considerable pleasure. He became a widower fifteen years ago, and the loss of an only son under tragic circumstances while at school left a permanent scar, although assuaged by the loyal and devoted care and companionship of his only daughter. Dr. Frier will be long remembered in his locality as an outstanding figure reminiscent of the Victorian era, a wise counsellor, a friend to everyone, and a practitioner who embodied all that is noble and fine in the medical profession.

Medico-Legal

CERTIFICATION WITHOUT SEEING PATIENT

[FROM OUR LEGAL CORRESPONDENT]

While her husband was a prisoner in Barlinnie Prison Mrs. George Black, of 11, Black Street, Glasgow, got his doctor to certify without seeing him that he was unfit on the usual National Health Service Act form stating: "I certify that I have examined you . . ." Mrs. Black told the doctor, who knew that Black's foot was in plaster and had hospital reports on his condition, that as her husband's foot was swelling he was staying at home. She did not reveal the fact that he was in prison. The doctor was prosecuted for granting medical certificates falsely stating that he had examined his patient. He was found not guilty in the Sheriff Court at Glasgow on July 14, but the Crown appealed. In the Scottish Justiciary Appeal Court the Solicitor-General said that if the Crown succeeded no further proceedings would be taken against the doctor, but the aim was to get the Court's ruling on whether the Sheriff-Substitute had been entitled to acquit him.

In his judgment (*Glasgow Herald*, October 10) Lord Clyde said that to certify that a patient had been examined when he had not was a contravention of the National Health Service (Scotland) Act. In the issue of a certificate authorizing the expenditure of public money laxity was to be deplored. No doubt partly with this in view the statutory form demanded not only a diagnosis but a statement that there had been an examination of the patient. The Sheriff-Substitute had not been entitled to find the doctor not guilty.

CRIMINAL ABORTION AND MANSLAUGHTER
SENTENCE REDUCED ON APPEAL

[FROM OUR LEGAL CORRESPONDENT]

On October 15 the appeal of Louis Aimee Newton against his sentence of three years' imprisonment for manslaughter and two years for unlawfully using an instrument to procure a miscarriage was heard by the Court of Criminal Appeal (*The Times*, October 15). Mr. Justice Ashworth at the trial had ordered the two sentences to run consecutively (*Journal*, May 24, p. 1242).

The Lord Chief Justice said that the consecutive sentences had been given for what was really the same offence, since it was the use of the instrument, and not any criminal negligence apart from that, which had caused the death. It was wrong in principle to give consecutive sentences for what was in effect one offence. Moreover, the judge in sentencing Newton had made it clear that he had it in his mind that Newton was a professional abortionist. There was no evidence whatever of that, and he ought to have been dealt with on the basis that it was an isolated case, although it was a serious offence. Accordingly the Court substituted sentences of 3 years' and 2 years' imprisonment concurrent for the consecutive sentences.

Newton's counsel told the Court that the proposed appeal against conviction had been abandoned on advice that the summing up at the trial could not properly be criticized.

BROADMOOR PATIENT TREATED AS SANE

[FROM OUR LEGAL CORRESPONDENT]

Frank Samuel Mitchell, aged 24, escaped from Broadmoor on July 8 (see *Journal*, July 19, p. 174) and robbed Mr. and Mrs. Peggs, of Wokingham, of clothes and a car and some money in furtherance of his escape, using violence towards them. After being at large for two days he was arrested in a Bournemouth-to-London motor coach at Hartley Witney. He was charged on October 2 at Reading Assizes with robbery with violence and pleaded guilty, asking through his counsel to be treated as a sane man (*The Times*, October 3).

Dr. Francis Brisby, the medical officer of Brixton Prison, said in evidence that although Mitchell was an aggressive psychopath he was not in his opinion certifiably insane. Mitchell at the age of 5 had been found to be of subnormal intellect, and was placed in the care of the L.C.C. He had greatly improved as a result of his treatment in Broadmoor, where he was sent in April, 1957, and was now in the process of maturing slowly, as could be seen from his progress educationally, emotionally, and in the ability to control his impulses. He had worked very hard to overcome the stigma of intellectual subnormality.

In sentencing Mitchell to life imprisonment Mr. Justice Byrne said that the medical evidence had satisfied him that Mitchell was sane and had been sane when he had committed these offences. The sentence of life imprisonment enabled the Secretary of State to review matters periodically and did not necessarily mean Mitchell would be in prison for the rest of his life.

Another Broadmoor patient, Clive Pickering, after being found unfit last June at York Assizes to plead to a murder charge, is now to stand his trial (*Daily Telegraph*, October 21). He is charged with the murder of John Frederick Boucher, aged 45, who died in the River Hull in May. After medical evidence at the Assizes, Pickering, aged 27, was ordered to be detained at Broadmoor. In a statement on October 20, Pickering's solicitor said: "We received two letters from Pickering. In view of the contents of the letters we made representations to the Secretary of State, and as a result Pickering will stand his trial."

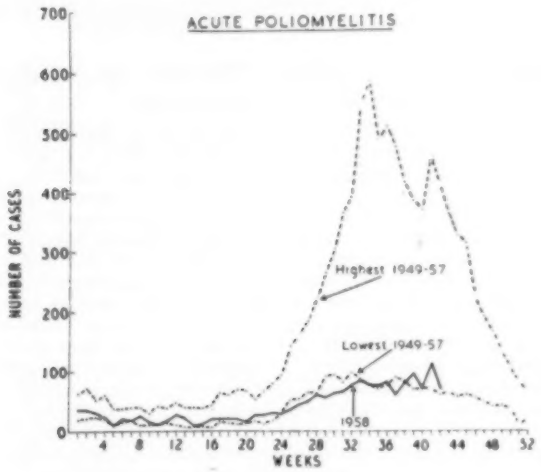
Vital Statistics

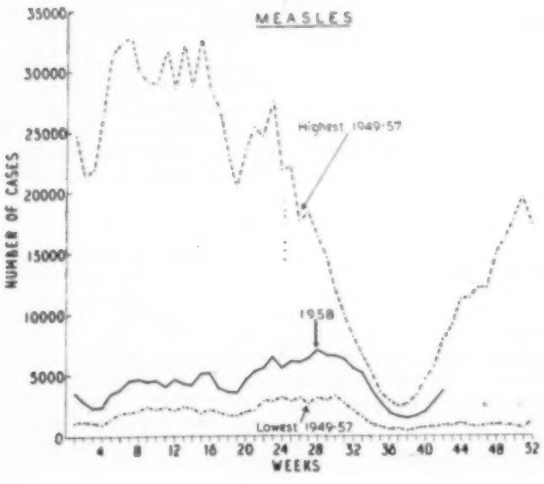
England and Wales in Third Quarter

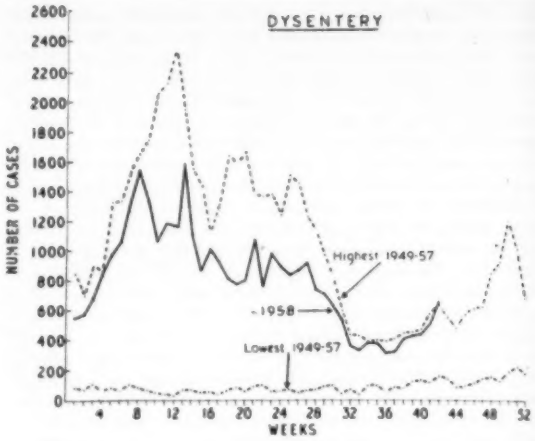
Live births numbered 180,167, giving a rate of 15.8 per thousand population, as compared with 15.9 in 1957 and 15.5 in 1956. Deaths numbered 105,547, giving a rate of 9.3 per thousand population. The rates in the September quarters of 1957 and 1956 were 9.7 and 9.3 respectively. The infant mortality rate, 19.8 per thousand live births, was again a record low figure for the quarter. The previous lowest for this quarter was 20.1, recorded in 1956. In 1938 the corresponding rate was 42.5. The stillbirth rate was 21.4 per thousand live and stillbirths; in the corresponding quarter of 1957 it was 22.4.

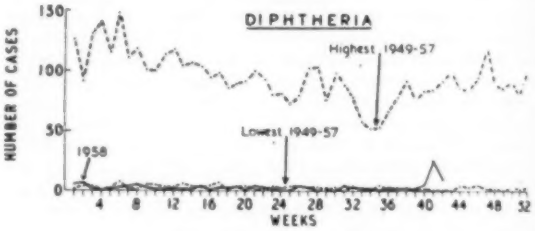
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus - - - - - -, the figures for 1958 thus ———. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending October 18

The increases in notifications of infectious diseases in England and Wales during the week ending October 18 included 961 for measles, from 2,778 to 3,739, 147 for scarlet fever, from 648 to 795, 146 for dysentery, from 512 to 658, 35 for acute pneumonia, from 216 to 251, and 30 for food-poisoning, from 229 to 259; the largest decreases were 43 for acute poliomyelitis, from 113 to 70, 24 for whooping-cough, from 500 to 476, and 15 for diphtheria, from 25 to 10.

10 cases of diphtheria were notified, 15 fewer than in the preceding week; 6 of these cases were notified in London (Finsbury 4, Islington 1, St. Pancras 1) and 2 in Barking M.B.

The largest rises in the incidence of measles were 114 for Yorkshire West Riding, from 306 to 420 (Halifax C.B. 104, Keighley M.B. 68); 109 in Yorkshire East Riding, from 110 to 219 (Kingston-upon-Hull C.B. 190), 94 in Middlesex, from 102 to 196 (Harrow M.B. 60), 83 in Kent, from 25 to 108 (Dover M.B. 68), 73 in Buckinghamshire, from 15 to 88 (Bletchley U.D. 87), 73 in Cheshire, from 176 to 249, 68 in Wiltshire, from 90 to 158 (Swindon M.B. 85). The largest increases in the notifications of scarlet fever were 31 in Lancashire, from 105 to 136, 29 in Yorkshire West Riding, from 77 to 106, 23 in London, from 47 to 70. The only large fluctuation in the returns of whooping-cough was a rise of 24 in Lancashire, from 47 to 71.

The notifications of acute poliomyelitis numbered 70, and these were 36 fewer for paralytic and 7 fewer for non-paralytic cases than in the preceding week. The largest returns were Lancashire 15 (Manchester C.B. 5, Liverpool C.B. 3), Yorkshire West Riding 9 (Huddersfield C.B. 3), London 7 (Shoreditch 2), Sussex 5 (Portslade-by-Sea U.D. 2, Shoreham-by-Sea U.D. 2).

The chief centres of dysentery were Yorkshire West Riding 123 (Leeds C.B. 32, Dearne U.D. 28, Ripon and Patley Bridge U.D. 21), London 73 (Islington 23), Hampshire 49 (Southampton C.B. 46), Lancashire 45 (Liverpool C.B. 21), Staffordshire 43 (Kidsgrove U.D. 41), Glamorganshire 34 (Rhondda M.B. 24), Northumberland 28 (Newbiggin-by-the-Sea U.D. 19), Warwickshire 28 (Coventry C.B. 18), Gloucestershire 27 (Bath C.B. 26), Nottinghamshire 26, Middlesex 25, Monmouthshire 23 (Newport C.B. 23).

MANAGEMENT OF PAIN

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Using the well established Droxalin formulation a new and exclusive manufacturing technique has produced in DROXALIN GEL an antacid possessing this significant increase in initial acid adsorption. The advantages of quicker acting DROXALIN GEL in peptic ulcer therapy and hyperacidity will be readily recognised. The palatability of Droxalin Tablets is achieved.

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ACTIVE INGREDIENTS	DOSAGE	PACKS AND PRICE
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INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **October 11** (No. 41) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria	25	15	2	0	2	1	0	6	0	1
Dysentery	512	69	213	22	5	210	19	55	12	2
Encephalitis, acute	2	1		0		13	2		0	
Enteric fever:										
Typhoid	4	3	0	0	1	5	2	0	0	1
Paratyphoid	3	0	1(B)	0	2(B)	5	0	0	2	
Food-poisoning	229	35	92	2		106	9	7	4	
Infective enteritis or diarrhoea under 2 years				14	31				7	33
Measles*	2,778	164	22	9	53	1,217	24	15	26	28
Meningococcal infection	14	1	13	0	2	38	5	10	1	
Ophthalmia neonatorum	34	7	6	0	1	24	0	3	0	
Pneumonia†	216	9	123	2	1	2,275	116	1047	57	1
Poliomyelitis, acute:										
Paralytic	83	1	22	0	7	68	0	15	5	5
Non-paralytic	30	0				26	1			
Puerperal fever§	253	36	15	1		354	50	6	10	1
Scarlet fever	648	47	114	20	15	336	27	49	13	27
Tuberculosis:										
Respiratory	484	62	76	16		494	51	101	12	
Non-respiratory	49	5	14	7		62	2	13	3	
Whooping-cough	500	26	74	58	35	317	17	24	0	19

DEATHS	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria	0	0	0	0	0	No comparable figures available.	0	0	0	0
Dysentery	1	0		0			0		0	
Encephalitis, acute		0			0		1			0
Enteric fever	0	0	0	0			0	0	0	0
Infective enteritis or diarrhoea under 2 years	1	0	2	1	0		0	0	1	0
Influenza	7	1	1	1	0		48	90	23	2
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	3		
Pneumonia	364	17	21	8	3		62	85	31	6
Poliomyelitis, acute	5	1	1	0	0		0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	70	9	7	1	2		7	13	3	3
Non-respiratory		1	1	0	0		1	1	0	0
Whooping-cough	1	0	0	0	0		0		0	0
Deaths 0–1 year	275	27	30	3	11		26	40	6	16
Deaths (excluding stillbirths)	8,760	696	503	91	142		912	829	169	169
LIVE BIRTHS	14,960	1239	516	235	388		1165	1021	227	437
STILLBIRTHS	296	24	28				21	25		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Nuffield Orthopaedic Centre.—At Oxford on October 27 QUEEN ELIZABETH THE QUEEN MOTHER opened a new building for teaching and research at the Nuffield Orthopaedic Centre. Professor J. TRUETA, its director, described the Centre in an article in the *Journal* in 1951 (April 28, p. 940). Two years ago Lord NUFFIELD added a further £200,000 to the £50,000 he had already given "to create in perpetuity an orthopaedic teaching centre under the guidance of the Nuffield professor of orthopaedic surgery in the University of Oxford," its main purpose being to offer facilities for training and research to young orthopaedic specialists, mostly from the Dominions, Colonies, and abroad. The new building substantially increases the Centre's facilities by providing a new and larger records office, clinical examination rooms, a department of radiology, and offices for the clinical consultants. But the most important addition is the new university department of orthopaedic surgery. Besides offices for the teaching staff and scholars, the department has laboratories for histology, pathology, electron-microscopy, and *x*-ray diffraction, together with a museum and an enlarged library. There are also residential quarters for some of the scholars in the grounds. A lecture hall for 140, a dining-room, and a common-room for the medical staff and scholars are among the features of this notable new example of Lord Nuffield's munificence. They combine to give the Centre more the aspect of a college.

Society of Medical Officers of Health.—The president of the Society, Dr. J. A. STIRLING, M.O.H. for Chesterfield, was in the chair at the annual dinner, held last week at the Royal College of Surgeons, Lincoln's Inn Fields. Proposing the health of the Society, Mr. DEREK WALKER-SMITH, the Minister of Health, spoke of two great contemporary social problems, old age and mental health. As to the latter, he said that the Government intended at an early date to introduce legislation to implement some of the recommendations of the Royal Commission on Mental Illness and Mental Deficiency, which would mean some further expansion of the health services of local authorities. The shift of emphasis to community care would result in more active prevention of illness, and in this the medical officer of health could play an important and distinguished part. Thanking medical officers of health for their splendid efforts in connexion with poliomyelitis immunization, the Minister said that by far the greatest share in those arrangements had fallen on the M.O.H., and very rapid progress had been made. Out of the total of 5¾m. people who had had two injections, 4m. had had their inoculations this year. The Ministry could really claim that its campaign had succeeded, but a still greater response from parents was needed. Nearly half the parents in this country had not seen fit to register their children for immunization, and there was a good deal more to do if all were to be vaccinated who should be. Dr. STIRLING, in his reply, looked back over the 40 years he had been in the public health service. Giving a word of warning about diphtheria, he said that they must still persevere with the mothers of to-day and see that the children got immunized. The three great public health problems were now atmospheric pollution, care of the aged, and mental health. Dr. G. H. GIBSON, toasting the guests, had hoped a recent annotation in the *Journal* (October 11, p. 904) would help him in his task, but, although he said this hope was not fulfilled, he appeared to have taken its grim warning very well to heart. Sir KENNETH COWAN, replying, struck an optimistic note and sent his hearers away confident that work of importance lay before the M.O.H.

Royal College of Surgeons of Edinburgh.—After the annual meeting of the College on October 15 it was announced that the following would hold office for the ensuing year: *President*, Professor JOHN BRUCE; *vice-presidents*, Professor NORMAN M. DOTT and Mr. WALTER W.

GALBRAITH; *secretary*, Mr. CHARLES W. A. FALCONER; *treasurer*, Mr. J. J. MASON BROWN; *president's council*, Mr. D. Band, Mr. R. S. Barclay, Mr. J. R. Cameron, Mr. I. L. Dick, Professor D. M. Douglas, Mr. E. L. Farquharson, Mr. A. J. C. Hamilton, Mr. J. N. J. Hartley, Professor R. J. Kellar, Mr. J. A. Ross, Professor G. I. Scott, Mr. J. A. Shepherd, and Mr. R. Leslie Stewart; *conservator of museum*, Professor D. E. C. Mekie; and *honorary librarian*, Dr. D. Guthrie.

F.R.C.S.Ed.—At a meeting of the Royal College of Surgeons of Edinburgh on October 15 the honorary fellowship was conferred upon Professor CHARLES B. HUGGINS, professor of surgery at Chicago University. At the same meeting the following candidates who passed the requisite examinations were admitted fellows:

J. Abrahamson, W. R. Allan, L. W. Baker, D. B. Berryman, K. S. Bhargave, N. Bhattacharyya, R. Cowley, S. J. Crews, P. J. E. Cruse, B. K. Datta, B. Dawka, N. C. Desai, H. Dovey, G. H. Dunstone, H. M. El-Sayed, K. D. Glass, G. D. Goel, A. J. Grant, P. Gupta, M. Habibulla, P. Harnarayan, F. W. Harrison, E. T. Heath, A. W. B. Heywood, H. K. Ismail, N. D. Jeyasekharan, M. J. Killingback, H. M. Learoyd, J. E. Lorang, M. H. Luntz, M. J. Lyons, M. M. A. Mahran, F. P. S. Marriott, P. R. Mehta, D. N. Menzies, R. E. Mickel, D. M. Millar, M. C. Misra, S. R. Mitra, B. C. Mukerjee, V. G. Muzumdar, D. W. Pfanner, R. Pringle, D. C. Provan, P. A. Rachow, J. A. Ryan, M. Sabetian, C. D. Sagar, K. M. Shah, R. P. Singh, J. G. Smith, J. H. Tait, C. F. Tham, T. T. Thomas, M. Vasudevan, N. H. Welsh, and T. Wilson.

Christmas Cards.—Unicef is once again launching its annual campaign to raise funds for its world-wide activities in the field of child welfare. The funds necessary for the organization's objectives are supplemented by the sale of its Christmas cards. A leaflet illustrating the cards is obtainable from Unicef Greeting Card Fund (Dept. C), 14–15, Stratford Place, London, W.1. These very decorative cards illustrate such themes as "Children Bearing Gifts," "A Time of Joy," and "Festive Times." Their cost is 7s. 6d. for ten cards. The subject of the Deaf Children's Society's Christmas card is "A Gay Winter Scene," designed by a deaf boy aged 11. Packets of six of these cards, with six Christmas seals, may be obtained for 3s. 6d. per packet from 1, Macklin Street, Drury Lane, London, W.C.2. The Muscular Dystrophy Group also offers Christmas cards for sale. They may be obtained in packets of six (from 2s. to 3s. a packet) from 34, Eccleston Square, London, S.W.1.

B.M.A. Clinical Meeting.—Details of the Sunday outings at the B.M.A. Annual Clinical Meeting next month at Southampton are given at p. 189 of the *Supplement*. This is to assist those registering for the meeting in choosing which outing they would like to attend.

R.S.M. Library.—The Royal Society of Medicine has been offered a grant of £24,000 by the Rockefeller Foundation for the general support of its library over the next five years. The Rockefeller Trustees make it clear that the grant is to help provide an adequate budget for the library while endowment for its continued maintenance is sought.

Leeds University.—Dr. D. B. BRADSHAW, lecturer in the department, has been appointed to the chair of public health. Dr. Bradshaw, who graduated in medicine from Dublin in 1932, is also deputy M.O.H. of Leeds. Among other appointments at Leeds are Dr. M. W. ATKINSON as tutor in psychiatry, Mr. R. G. BURWELL as lecturer in anatomy, Dr. A. J. KENNY as lecturer in biochemistry, Dr. N. R. ROWELL as tutor in dermatology, and Mr. F. G. SMIDDY as lecturer in surgery.

Professor W. A. Bain has resigned the chair of pharmacology at Leeds University on his appointment as director of the Smith Kline and French Research Institute. The institute, which is expected to be completed next summer, is at Welwyn Garden City.

Professor Ian Aird has been elected an honorary fellow of the Swedish Surgical Society, and has been awarded the society's Olof Af Acrel medal.

Chair of Social Medicine, Otago.—Dr. C. W. DIXON, reader in epidemiology in the department of preventive medicine and public health at Leeds, has been appointed to the chair of social and preventive medicine at Otago University. Dr. Dixon qualified from King's College Hospital in 1935, later proceeding M.D. London. Previously he was an M.O.H. in the New Zealand Government Service and a W.H.O. medical consultant on smallpox.

COMING EVENTS

Institute of Dermatology.—Semi-permanent exhibition, November 5 to 26, on "The Skin and Friction."

Robert Jones Lecture.—Mr. NORMAN CAPENER will lecture on "Spondylolisthesis: Spinal Strain" on November 13 at 5 p.m. at the Royal College of Surgeons, Lincoln's Inn Fields.

Institute of Laryngology.—Annual address will be given by Mr. T. G. WILSON on "The Modern Treatment of Deafness in Historical Perspective" on November 14 at 4.30 p.m. The institute will be "At Home" to medical visitors from 2 p.m. The joint annual dinner of the institute and the associated Royal National Throat, Nose, and Ear Hospital will be held the same evening at University College, Gower Street, London, W.C.1.

Institute of Diseases of the Chest.—Panel discussion for general practitioners on "Virus Infections of the Respiratory Tract," December 2, at 2.30 p.m. at the Brompton Hospital, London, S.W.3. Practitioners wishing to attend should notify the dean.

British Institute of Radiology.—Annual congress and exhibition, December 4 and 5. Details from the general secretary of the Institute, 32, Welbeck Street, London, W.1.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

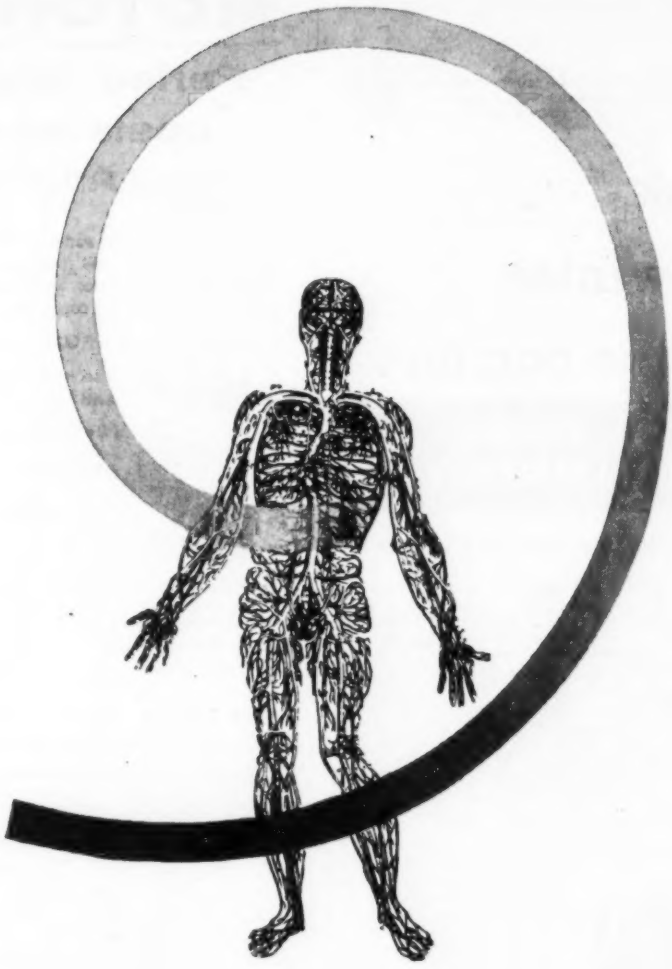
The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

British Heart Journal.—Issued quarterly (£3 annually). The new issue, Vol. 20, No. 4, includes:

THE ORIENTATION OF THE HEART AND THE APPEARANCE OF ITS CHAMBERS IN THE ADULT CADAVER. Robert Walmsley.
SELECTIVE CINÉ-ANGIOCARDIOGRAPHY WITH IMAGE INTENSIFICATION. Hamish Watson, C. Pickard, K. G. Lowe, and Ian Hill.
THE CORRELATION BETWEEN VARIOUS ASSESSMENTS OF PULMONARY ARTERIAL PRESSURE IN MITRAL STENOSIS. J. F. Boyd, S. D. Scott Park, and George Smith.
THE FUNCTIONAL AND CLINICAL ANATOMY OF THE MITRAL VALVE. J. C. Van Der Spuy.
RESIDUAL LUNG VOLUME IN MITRAL DISEASE. R. Garbagni, P. F. Angelino, A. Brusca, and E. Minetto.
THE ELECTROCARDIOGRAM IN SYPHILITIC HEART DISEASE. Geoffrey Storey.
THE ELECTROCARDIOGRAM IN PECTUS EXCAVATUM. Jorge Martins de Oliveira, Mohinder P. Sambhi, and Henry Zimmerman.
MODIFICATION OF VENTRICULAR GALLOP RHYTHM INDUCED BY POOLING OF BLOOD IN THE EXTREMITIES. James J. Leonard, Arnold M. Weissler, and James V. Warren.
THE AORTIC LESION OF ANKYLOSING SPONDYLITIS. B. M. Ansell, E. G. L. Bywaters, and I. Doniach.
THE CEREBRAL BLOOD FLOW IN MITRAL STENOSIS AND ITS RESPONSE TO CARBON DIOXIDE. H. A. Dewar and L. A. G. Davidson.
THE EFFECT OF VALVOTOMY ON THE MURMURS OF PULMONARY AND AORTIC STENOSIS. Bertrand G. Wells.
PULMONARY HYPERTENSION IN CONGENITAL HEART DISEASE. William Evans and D. S. Short.
FOETAL PAROXYSMAL AURICULAR TACHYCARDIA. C. W. Kesson.
THE VASOCONSTRICTIVE FACTOR IN PULMONARY HYPERTENSION. Paul Wood.

British Journal of Venereal Diseases.—Issued four times a year (£3 annually). The new issue (Vol. 34, No. 3) includes:

FIGURES AND FANCIES. S. M. Laird.
GUMMATOUS OSTEITIS OF THE SKULL. W. V. Macfarlane and Ian Rannie.
THROMBOSIS OF THE POSTERIOR INFERIOR CEREBELLAR ARTERY OF LUETIC AETIOLOGY. R. V. Rajam, N. Vasudeva Rao, and P. N. Rangiah.
LYMPHOGRANULOMA VENEREUM. A REVIEW OF 61 CASES. David Erskine.
CANDIDA ALBICANS URETHRITIS. REPORT OF A CASE. W. Fowler.
STUDIES ON THE EFFECT OF VARIATION OF CONCENTRATION AND ORIGIN OF LECITHIN (NATURAL AND SYNTHETIC) IN CARDIOLIPIN COMPLEMENT-FIXATION ANTIGEN. Alice Reyn and Michael Weis Bentzon.
SACRO-ILIITIS IN REITER'S DISEASE. J. K. Oates.
STUDIES IN PROSTATITIS. Edward Gartman.
DIAGNOSIS OF TRICHOMONAS VAGINALIS URETHRITIS IN THE MALE AS A ROUTINE CLINIC PROCEDURE. C. S. Nicol.
PENICILLIN TREATMENT FAILURES IN MALE GONORRHOEA. Neil L. Dallas.
REITER'S PROTEIN COMPLEMENT-FIXATION TEST. REPORT OF A TRIAL IN 1,000 UNSELECTED CASES. W. D. Foster, C. S. Nicol, and A. H. Stone.



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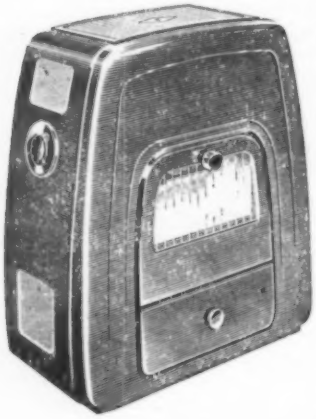

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SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, November 3

DENTAL AND MEDICAL SOCIETY FOR THE STUDY OF HYPNOSIS.—At Trocadero Restaurant, 7.15 p.m., annual dinner, Dr. D. Keir Fisher: Anaesthesia—the Anaesthetist—and You.

GUY'S HOSPITAL.—At Anatomy Lecture Theatre, 5.15 p.m., lecture-demonstration in endocrinology by Dr. P. M. F. Bishop: Hypothyroidism.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Heath Clark Lecture by Dr. Karl Evang (Norway): Health Service, Society and Medicine; Present-day Health Services in their Relation to Medical Science and Social Structure—Introduction—Main Types of Existing Health Services.

MARLBOROUGH DAY HOSPITAL.—8.15 p.m. Dr. Louis Minski: Psychosomatic Problems.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. B. Ackner: Psychogenic Pain.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., Dr. J. R. Postgate: Sulphur Bacteria—Oxidative Stages of the Bacterial Sulphur Cycle.

Tuesday, November 4

FOUNTAIN HOSPITAL.—5.30 p.m., Dr. J. Tizard: Impressions of Work in Mental Deficiency in the U.S.S.R.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. F. Borrie: Cutaneous Vascular System.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, 3 p.m., Guest lecture by Dr. J. Goodwin: Heart Disease and Pregnancy.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Heath Clark Lecture by Dr. Karl Evang (Norway): Health Service, Society and Medicine; Present-day Health Services in their Relation to Medical Science and Social Structure—Role of the Hospital.

MANCHESTER UNIVERSITY: DEPARTMENT OF OCCUPATIONAL HEALTH AND NORTH-WEST ENGLAND FACULTY, COLLEGE OF GENERAL PRACTITIONERS.—At Theatre 1, Clinical Sciences Building, York Place, 8.30 p.m., Radiation Hazards in Modern Industry.

ST. ANDREWS UNIVERSITY.—At Physiology Lecture Theatre, 6 p.m., Dr. G. L. Jackson (U.S.A.): Biologically Based Dentistry.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Mr. Roger de Vere: Fibrinoids and Allied Tumours.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, Gower Street, W.C., 5.30 p.m., Professor J. F. Danielli, F.R.S.: Generalized Cell Theory and its Relevance to Certain Problems of Drug Action.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. Colin Edwards: neurological demonstration.

Wednesday, November 5

ASSURANCE MEDICAL SOCIETY.—At Medical Society of London, 5 p.m., Dr. J. Maurice Campbell: Life Assurance for those Applicants with Heart Disease.

COLLEGE OF GENERAL PRACTITIONERS: NORTHERN HOME COUNTIES FACULTY.—At the George Hotel, Enfield, 8.30 p.m., symposium: Research in General Practice.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Subcutaneous Infections due to Fungi.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. Paul Wood: Bedside Techniques in Cardiology.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Dr. I. Friedmann, Dr. D. A. Osborn, and Dr. A. Jeanes: clinical pathological conference.

INSTITUTE OF UROLOGY.—At Royal College of Surgeons of England, 5 p.m., Clifford Morson Lecture by Professor C. Dent: Metabolic Causes of Renal Stone Formation.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Heath Clark Lecture by Dr. Karl Evang (Norway): Health Service, Society and Medicine; Present-day Health Services in their Relation to Medical Science and Social Structure—Role of the General Practitioner.

MANCHESTER MEDICAL SOCIETY: SECTION OF MEDICINE.—At Large Anatomy Theatre, Medical School, Manchester University, 5 p.m., Dr. P. J. D. Snow: The Carcinoid Syndrome. Dr. D. Longson: Adrenal Hyperfunction.

MIDLAND MEDICAL SOCIETY.—At Birmingham Medical Institute, 8.15 p.m., Dr. P. H. Davison: Management of Chronic Cardiac Failure.

●NATIONAL COLLEGE OF RUBBER TECHNOLOGY, Northern Polytechnic, Holloway Road, N.—6.30 p.m., Dr. J. T. Scales: Synthetic Materials in Orthopaedics.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Guest lecture by Dr. G. M. McGowan: Potassium Metabolism.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. A. B. Stewart: London County Council Health Services.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE: EDINBURGH BRANCH.—At West Medical Theatre, Edinburgh Royal Infirmary, 5 p.m., Professor G. W. A. Dick: Tropical Viruses.

Thursday, November 6

FACULTY OF HOMOEOPATHY.—At Royal London Homoeopathic Hospital, 5 p.m. Richard Hughes Memorial Lecture by Dr. D. M. Gibson: Aetiological Aspects of Homoeopathic Materia Medica.

LIVERPOOL UNIVERSITY: FACULTY OF MEDICINE AND LIVERPOOL MEDICAL INSTITUTION.—Surgery Theatre, Old Medical School, 5.15 p.m., Joint History of Medicine Lecture by Dr. W. Brockbank: The Ancient Art of Enema Administration.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Heath Clark Lecture by Dr. Karl Evang (Norway): Health Service, Society and Medicine; Present-day Health Services in their Relation to Medical Science and Social Structure—Role of Drugs. At Royal Society of Medicine, 5 p.m., Semon Lecture by Professor L. Rüedi (Zurich): Some Observations on the Histology and Functions of the Larynx.

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH.—5 p.m., John Matheson Shaw Lecture by Dr. W. M. Arnott: Climate of Medical Education.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Bradshaw Lecture by Dr. K. W. Donald: Heart Disease and Exercise.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Desmond Curran: postgraduate demonstration in psychiatry.

UNIVERSITY COLLEGE LONDON.—At Anatomy Theatre, Gower Street, W.C., 1.15 p.m., Dr. D. Wilkie, Ph.D.: Aims of Sexual Reproduction.

Friday, November 7

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. T. Brain: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. N. Pattinson: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners by Mr. G. H. Howells: Sinusitis.

LIVERPOOL UNIVERSITY: FACULTY OF MEDICINE.—At Large Lecture Theatre, New Medical School, Ashton Street, 5.15 p.m., McMurray Lecture in Orthopaedic Surgery by Professor W. P. Blount (Wisconsin): Fractures in Children.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Heath Clark Lecture by Dr. Karl Evang (Norway): Health Service, Society and Medicine; Present-day Health Services in their Relation to Medical Science and Social Structure—Public Health Service.

MANCHESTER MEDICAL SOCIETY.—At Clinical Sciences Building, York Place, 4.30 p.m., Sir Roy Cameron, F.R.S.: The Principle of Reversibility in Liver Pathology.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Guest lecture by Mr. A. S. Kerr: Relief of Pain.

●ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS.—4 p.m., William Blair-Bell Memorial Lecture for 1958 by Dr. J. M. Crawford: Study of Placental Growth in Normal Pregnancy and in Erythroblastosis Foetalis.

ROYAL MEDICO-CHIRURGICAL SOCIETY OF GLASGOW.—At Royal Faculty of Physicians and Surgeons of Glasgow, 8.30 p.m., (1) Mr. T. Gibson: Domestic Burns—Their Prevention and Treatment. (2) Mr. I. MacGregor: Changing Pattern of Treatment in Hand Infections.

ROYAL SOCIETY OF HEALTH.—At Newe Lecture Theatre, Newcastle upon Tyne, 10.30 a.m., Symposium on Atmospheric Pollution. Professor G. R. Clemo, F.R.S.: Chemistry of Cigarette Smoking and its Possible Implications; Dr. A. G. Ogilvie: Chronic Bronchitis in Newcastle upon Tyne; Mr. L. Mair: Second Appointed Day on Tyneside.

Saturday, November 8

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—11.30 a.m., Guest lecture by Professor L. Rüedi (Zurich): New Developments in the Surgery of Otosclerotic Diseases.

APPOINTMENTS

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—B. H. Hand, M.S., F.R.C.S., Consultant Surgeon, Ipswich and East Suffolk Hospital; M. D. Mehta, M.B., B.S., F.F.A.R.C.S., Consultant Anaesthetist, King's Lynn Area; Margaret M. Downes, M.B., Ch.B., M.R.C.O.G., Part-time Consultant Obstetrician and Gynaecologist, Lowestoft and Great Yarmouth Hospitals; M. F. T. Yealland, M.B., B.Chir., M.R.C.P., Consultant Neurologist, United Cambridge Hospitals and Regional Board Hospitals; J. P. Hughes, M.B., B.S., M.R.C.P., Senior Medical Registrar, Ipswich and East Suffolk Hospital; A. R. Walker, M.B., B.S., Registrar in Psychiatry, St. Andrew's Hospital; M. K. Basu Mallick, M.B., B.S., D.Obst.R.C.O.G., Registrar in Obstetrics and Gynaecology, Peterborough Group of Hospitals; Sheila M. Griffiths, M.B., B.S., Registrar in Geriatrics, Ipswich and East Suffolk Hospital Group; M. A. Jafri, M.B., B.S., D.T.M.&H., Medical Registrar, Peterborough Hospital Group; P. R. H. Slade, Ch.M., F.R.C.S., Senior Registrar in Thoracic Surgery, Papworth Hospital; I. B. Munro, M.B., Ch.B., F.R.F.P.S., M.R.C.P., M.R.C.P.Ed., Senior Medical Registrar, United Norwich Hospitals; J. Ludbrook, M.B., Ch.B., F.R.C.S., Surgical Registrar, Norfolk and Norwich Hospital; S. P. Kumar, M.B., B.S., D.O.M.S., D.O., Ophthalmic Registrar, Norfolk and Norwich Hospital; Miss F. Husain, M.B., B.S., and W. S. Sykes, B.M., B.Ch., Anaesthetic Registrars, Ipswich and East Suffolk Hospital; Hazel M. Wilson, M.R.C.S., L.R.C.P., Registrar in Mental Deficiency and Child Psychiatry, Little Plumstead Mental Deficiency Group of Hospitals, and Child Psychiatry Service.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Bexon.—On October 10, 1958, at Dryburn Hospital, Durham, to Muriel, wife of Dr. Wallace H. Bexon, of Grange Farm Cottage, Durham, a sister for Fiona—Alison.

Gordon.—On October 17, 1958, at Sale, Victoria, Australia, to Drs. Nesta and William F. Gordon, a son.

Lovel.—On September 29, 1958, to Joan (formerly D'Arcy), M.D., D.C.H., and Lester Lovel, of 46, The Ridge Way, Sanderstead, Surrey, a son—Paul D'Arcy.

Palfrey.—On October 22, 1958, at University College Hospital, London, W.C., to Ann and John Palfrey, of University College, Ibadan, Nigeria, a brother for Michael and Susan—Christopher Mark.

Perry.—On October 19, 1958, at the County Hospital, Haverfordwest, to Dr. Elizabeth Perry (formerly Thomas), wife of Dr. Lynn Perry, a daughter, sister for William and David.

DEATHS

Chubb.—On September 28, 1958, at Kenilworth, Cape Town, South Africa, Elsie Mary Chubb, M.D., D.P.H.

Clark.—On October 6, 1958, at 6, Heanderland Road, Edinburgh, Katherine Jane Stark Clark, M.D., D.P.H., aged 92.

Eaton.—On October 8, 1958, Douglas Arthur Tighe Eaton, L.R.C.P.&S.I. & L.M., of Whole Farm Cottage, Stone-in-Oxney, Tenterden, Kent, late of South Benfleet, Essex.

Homan.—On September 27, 1958, William Travers Homan, L.M.S., L.M., of Donegan, Portland Road, Greystones, Eire, late of Dover, Kent.

Hughes.—On September 20, 1958, David Morgan Hughes, F.R.C.S., of 24, West End Avenue, Pinner, Middx, aged 82.

Murison.—On September 28, 1958, at Trotton Old Rectory, Rogate, Sussex, Taylor David Murison, L.R.C.P.&S.Ed., L.R.F.P.S., Lieutenant-Colonel, I.M.S., retired.

Prager.—On September 29, 1958, Gertrude Anna Prager, M.D., of Manchester, aged 47.

Seingry.—On September 26, 1958, at Llandough Hospital, Heinrich Egon Seingry, M.B., B.Ch., of 4, Danycoed Road, Cardiff, aged 48.

Wanhill.—On September 29, 1958, at Broadstone, Dorset, Charles Frederick Wanhill, M.R.C.S., L.R.C.P., D.P.H., Lieutenant-Colonel, R.A.M.C., retired, aged 86.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Abortion and Bicornuate Uterus

Q.—*Is hormonal treatment indicated during pregnancy in a woman who has a bicornuate uterus and a history of repeated miscarriages?*

A.—The incidence of abortion, and of premature labour, is raised when the uterus is malformed, probably either because the abnormal organ cannot grow and stretch normally, or because of inadequate placentation (especially if sited on the spur or septum between the horns), or both. Theoretically hormone therapy with oestrogen and progesterone might counter these factors to some degree, for the prognosis for a viable baby seems to improve with successive pregnancies, but in practice such therapy has not yet been shown to be effective. In general the prognosis is better the greater the degree of imperfect fusion (e.g., better in uterus didelphys than bicornis). Nevertheless, gross degrees of bicornuity are sometimes corrected between pregnancies by the reconstructive operation of utriculoplasty, but in minor degrees the operation is difficult and of doubtful value.

Risk of Meningocele

Q.—*What are the risks of malformation in further children of a young couple who have already had two children born with a meningocele?*

A.—The risks for a further child after a mother has had two children with meningocele are not yet accurately known. The risk after one such child is of the order of 1 in 25,[1] and the risk is probably further increased when two such children have been born. A small personal series indicates a risk of about 1 in 10. The risk is probably somewhat modified by the part of the country in which the parents live, and by the parents' social class.

REFERENCE

1 MacMahon, B., Pugh, T. F., and Ingalls, T. H., *Brit. J. prev. soc. Med.*, 1953, **7**, 211.

Oral Contraceptives

Q.—*What is the latest information about oral contraceptives?*

A.—Data of a kind which can be appraised critically are available on two oral contraceptive agents. In a trial in Puerto Rico, directed by Dr. Gregory Pincus, and referred to in an annotation in the *Journal*,[1] the steroid known as "enavid" administered in a dose of 10 mg. daily for 20 days, beginning on the 5th day of each menstrual cycle, proved 100% effective in preventing conception in those volunteers who omitted no tablets while under treatment. The mechanism involved is inhibition of ovulation, which some might regard as potentially dangerous if long continued, and particularly if children were desired at a later date. Further drawbacks to this method are its costliness, the need for regular daily treatment in 20-day courses, and the intolerance to the drug which a proportion of women show. None of the patients in the trial had any untoward effects from the treatment.

The second agent is *m*-xylohydroquinone, which Sanyal[2–5] considers to be the antifertility factor of pea oil, acting by virtue of its anti-progesterone and anti-vitamin E effects. This has been tested fairly extensively in India, the patients taking a capsule of 300–350 mg. on the 16th and 21st days of the cycle—that is, twice a month only. A significant reduction in fertility rates has been observed—but to the extent only of reducing them by about half, so that this agent would appear to be far less effective than enavid.

It is encouraging that a good deal of high-quality research into the problem of devising the ideal contraceptive is now being undertaken by first-class investigators, and, though "the pill," in its ideal form, is probably still a long way off, optimism would appear to be not unwarranted.

REFERENCES

1 *Brit. med. J.*, 1958, **2**, 297.
2 Sanyal, S. N., *Acta endocr. (Kbh.)*, 1956, suppl. 28, 72.
3 —— and Ghosh, S., ibid., 1956, suppl. 28, 83.
4 —— Banerjee, S. C., and Sen, J., ibid., suppl. 28, 93.
5 —— ibid., suppl. 28, 98.

High-fat Reducing Diet

Q.—*In view of recent work showing the efficacy of high-fat reducing diet, what percentage of fat, carbohydrate, and protein should the average reducing diet contain?*

A.—Some of the recent work in relation to high-fat reducing diets has related only to diets suitable for experimental purposes.[1–3] Others, notably Pennington,[4 5] have used similar diets to reduce obese patients, apparently with success. There is at the moment no fixed agreement as to the relevant portions of fat, carbohydrate, and protein, but the usual practice in reducing diets is to diminish the carbohydrate intake and thus to increase the relative proportions of fat and protein. These latter can be increased if the resulting diet is unsatisfactory.

REFERENCES

1 Kekwick, A., and Pawan, G. L. S., *Arch. Middx Hosp.*, 1953, **3**, 139.
2 —— —— *Lancet*, 1956, **2**, 155.
3 —— —— *Metabolism*, 1957, **6**, 447.
4 Pennington, A. W., *Delaware St. med. J.*, 1951, **23**, 79.
5 —— *Amer. J. dig. Dis.*, 1955, **22**, 33.

NOTES AND COMMENTS

Intestinal Hurry.—Dr. IAN STEWART (Keighley) writes: In the advice on intestinal hurry ("Any Questions?" October 4, p. 868) there is the sentence: "In severe dysentery morphine by injection may greatly help the patient, but it can only be used once or twice." In infections with Shiga's bacillus and the presence of a powerful exotoxin, I would have thought that morphine by injection was extremely dangerous. During the 12 years I was working with this group of diseases no form of opium was used until the diagnosis was established.

OUR EXPERT replies: Opium has been used for over 200 years with benefit in the treatment of dysentery. Manson-Bahr[1] says nothing against its use, and morphine is strongly recommended by Strong.[2] In extensive experience with cases of dysentery I have used morphine as described in patients whose diarrhoea and pain were severe. No ill effects occurred and the patients were always greatly relieved.

REFERENCES

1 Manson-Bahr, P., *The Dysenteric Disorders*, 1943, 2nd ed. Cassell, London.
2 Strong, R. P., *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases*, 1945, 7th ed. H. K. Lewis, London.

Correction.—In the article on "Sedatives and Tranquillizers" by W. Sargant (*Journal*, October 25, p. 1031) the dose of bromide in the paragraph headed "Bromides" should have been 20–30 gr., not 20–30 mg.

Collected Articles from the "British Medical Journal"

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